DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR FISCAL YEAR 2018

WEDNESDAY, MARCH 8, 2017

U.S. SENATE,
SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 10:30 a.m., in room SD–138, Dirksen Senate Office Building, Hon. Roy Blunt (chairman) presiding.

Present: Senators Blunt, Cochran, Alexander, Moran, Rubio, Murray, Durbin, and Leahy.

SAVING LIVES THROUGH MEDICAL RESEARCH

OPENING STATEMENT OF SENATOR ROY BLUNT

Senator BLUNT. The Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies will come to order.

Good morning. I want to thank our witnesses for appearing before this subcommittee today. In the next few years as we continue to confront difficult spending choices, we really have to continue, in my view, to firmly establish our Federal commitment to the National Institute of Health (NIH).

Since its founding, the NIH has funded research to raise life expectancy, to lower healthcare costs, and to improve the quality of life for all Americans.

In the 80 years since Congress established the National Cancer Institute, we've gone from crude treatments with grim prognosis to a place where we know much more about what we are dealing with and how to deal with it. And we are going to hear today some future projections of how that even advances in a more dramatic way.

Since the 1940s, the rate of cardiovascular deaths have dropped 60 percent thanks to effective treatments, a lot of which involved NIH funded research. These are really two great examples, both in cancer and in cardiovascular disease, of what happens when you have the kinds of medical breakthroughs that we've seen and I think can see in even greater numbers.

In the past year, NIH funded the development of an artificial pancreas that would be life changing if you have Type I diabetes. They have discovered biomarkers that were unique to two different prostate cancer stages and decoded the structure of the Zika virus.

We need to remember that this progress didn't occur on its own. It happened because of generations of researchers funded largely by the U.S. Government through the NIH tirelessly worked to discover the science that led to these treatments and cures. Federal funding was an essential component of that progress and has advanced the understanding of disease, raised life expectancy, and improved quality of life for patients and their families.

Last year for the first time in over a decade, the Labor/HHS Appropriations Bill significantly increased funding for NIH. This $2 billion increase allowed the NIH to fund 1,147 more grants nationwide than they would have funded otherwise. Funding for NIH research in my home State increased by $37.4 million or 8 percent as we saw just about that same size increase in overall NIH funding.

Consistent, sustained increases in funding are critical for biomedical researchers as they undertake the complex multiyear studies necessary to pursue new treatments. Consistent funding is also essential if we are going to encourage young researchers. We are going to hear some about that today, as well to really believe that they can and will be able to make a real difference in research.

By the way, a pattern has to first happen in the second year. And I want to thank Senator Murray for her support and leadership as we, again, finish the bill that is still pending before the Congress to add another $2 billion to the basic research funding at NIH. The fiscal year 2016 funding increase cannot and should not be seen as a one-time thing or even towards some goal that is anywhere short of funding research as long as there's research that is promising to be funded.

We do know that the scientific advances that will be made in the next 10 years can make a real difference in people's lives and make a real difference in overall healthcare cost. They'll make a real difference in taxpayer funded healthcare costs. We need to be committed in that regard. And certainly, Senator Murray has been and we've been able to work together on this. Senator Murray, I would like to turn to you for your opening remarks.

[The statement follows:]

PREPARED STATEMENT OF SENATOR ROY BLUNT

Good morning. I want to thank our witnesses for appearing before the Subcommittee today.

In the next few years, as we continue to confront difficult spending choices, we must continue to firmly establish our Federal commitment to the National Institutes of Health (NIH). Since its founding, the NIH has funded research to raise life expectancy, lower healthcare costs, and improve the quality of life for all Americans. In the 80 years since Congress established the National Cancer Institute, crude treatments and grim prognoses have been replaced by individualized treatments and sophisticated diagnostics. Since the 1940s, the rate of cardiovascular disease deaths has dropped 60 percent thanks to effective treatments developed by NIH-funded research. And these great strides are just two examples of thousands of medical breakthroughs. In just the past year, NIH funded the development of an artificial pancreas that would be a life-changing advance for many people with type 1 diabetes; discovered biomarkers that were unique to two different prostate cancer stages; and decoded the structure of the Zika virus.

We should remember that this progress did not occur on its own. It happened because generations of researchers, funded largely by the U.S. Government through the NIH, tirelessly worked to discover the science that led to these treatments and cures. Federal funding was an essential component of the progress that has ad-

vanced the understanding of disease, raised life expectancy, and improved the quality of life for patients and their families.

Last year, for the first time in over a decade, the Labor/HHS Appropriations bill significantly increased funding for the NIH. This $2 billion increase allowed the NIH to fund 1,147 more grants nationwide. Funding for NIH research in my home State of Missouri has increased $37.4 million or 8 percent. Consistent, sustained increases in funding are critical for biomedical researchers as they undertake the complex, multi-year studies necessary to pursue new treatments and cures. But the way to begin a pattern is in the second year, and, with my thanks to Senator Murray for her support, this fiscal year we were able not only to pass the first bipartisan Labor/HHS bill out of Committee in 7 years, but also to increase NIH funding by another $2 billion.

The fiscal year 2016 funding increase cannot and should not be a one hit wonder. We should not point to that and believe we have accomplished our goal. We must remain focused on establishing a pattern of responsible investment through the appropriations process. We do not know the scientific advances that will be made in the next 10 years, but we do know that if we keep investing in NIH, they will keep making life-saving breakthroughs. That is why funding NIH, every year, through the appropriations process, provides the opportunity to capitalize on and enhance the discoveries made by the research community and ensure we are funding the right programs with the most scientific promise.

I look forward to hearing from today's witnesses who understand, first hand, the importance of NIH funding and the impact this funding has on the lives of every American.

Thank you.

STATEMENT OF SENATOR PATTY MURRAY

Senator MURRAY. Well, thank you very much, Mr. Chairman, for calling this hearing and I want to thank all of our witnesses for traveling here today and being with us. I look forward to hearing what you have to say.

The investments that we make in this subcommittee help keep families and communities healthy by supporting programs that reduce infant mortality, train our doctors and nurses, provide care in rural communities, and prevent the spread of infectious diseases and so much more.

The NIH accounts for the largest share of our subcommittee's resource and its work is vital to all those efforts. The basic research it supports leads to the discoveries and breakthroughs that give hope to those living with chronic and life threatening disease and bolster economic growth and competitiveness.

Today NIH researchers are taking advantage of the achievements made in human genetics, imaging technology, and other fields to advance our understanding of diseases like cancer and Alzheimer's. Its precision medicine initiative is using the genetics of cancer to find effective therapies while its BRAIN Initiative is revolutionizing our understanding of the human brain.

We are on the cusp of major breakthroughs for so many illnesses that cost lives and hurt families each day.

But now there are efforts that actually would put millions of Americans' access to these advanced treatments at risk and there is a very real threat to this committee's ability to fund future increases NIH to sustain its research efforts.

Republicans are, as we speak, rushing to dismantle the Affordable Care Act which expanded health coverage to 20 million Americans and ended the restrictions on preexisting conditions and lifetime caps that previously forced many of those who had serious illnesses to choose between bankrupting their families or foregoing treatment.

The House Republican Trump Care Bill would take us back to those bad days, meaning people across the country could lose access to the actual treatments that NIH research makes possible.

When I consider what that would mean, I think of one of my guests at the President's address last week, Marci Owens. She's from Seattle and her mother died at the age of 27. Her mother was 27 years old. She became ill. She lost her job and she lost her health insurance, and eventually died.

And I am very deeply troubled that some Republicans want to return it to a time when there are more stores like Marci's.

I recently heard from the wife of a father in a self employed contractor named Richard in my home State of Washington who, thanks to the ACA, had health insurance through Medicaid when he was diagnosed with an aggressive and rare form of leukemia.

His illness didn't respond to the conventional therapy, so his doctors with the Seattle Cancer Care Alliance enrolled him in a CAR T cell immunotherapy trial in a last-ditch effort. Richard is now in remission with real hope for a long-term cure. And his family says the immunotherapy treatment saved his life. Absent the ACA, Richard's wife, Jennifer, says she believes she would now be raising their two children on her own.

I am also concerned by the details of the President's budget that the administration recently chose to make public. Cutting non-defense spending by $54 billion would require devastating cuts to the education, health, and training programs that this subcommittee funds. And I don't see how NIH, which accounts for 20 percent of the funding in the bill will avoid being affected. I know members on both sides of the aisle here agree on the importance of medical research, so this is not a partisan issue.

Just last December, Democrats and Republicans were able to come together to establish a new $4.8 billion funding stream for NIH and I want to thank the chairman for his focus on that last year to help accelerate medical research efforts. That was an important step forward as was the bipartisan spending bill that this subcommittee wrote last spring that would provide additional funding for NIH and other priorities in 2017. Unfortunately, we know now the fate of that spending bill is uncertain.

Patients and families across the country are waiting. They're hoping for better cures and treatments as well as for help with the other challenges they face, whether it is quality child care or paying for college or getting care when they're sick. And here in Congress, I hope we can do our part to deliver. So thank you very much, Mr. Chairman.

[The statement follows:]

PREPARED STATEMENT OF SENATOR PATTY MURRAY

Thank you, Mr. Chairman, for calling this hearing.

And welcome Doctors Eberlein, Grabowski, Sasser, and Schultz-Cherry.

I look forward to the discussion this morning.

The investments we make here in this subcommittee help keep families and communities healthy, by supporting programs that:

—reduce infant mortality,

—train doctors and nurses,

—provide care in rural communities,

—prevent the spread of infectious diseases,

—and so much more.

The NIH accounts for the largest share of our subcommittee's resources, and its work is vital to these efforts.

The basic research it supports leads to the discoveries and breakthroughs that:
—give hope to those living with chronic and life-threatening disease;
—and bolster economic growth and competitiveness.

Today, NIH researchers are taking advantage of the achievements made in human genetics, imaging technology, and other fields to advance our understanding of diseases like cancer and Alzheimer's disease.

Its Precision Medicine Initiative is using the genetics of cancer to find effective therapies, while its BRAIN Initiative is revolutionizing our understanding of the human brain.

We're on the cusp of major breakthroughs for so many of the illnesses that cost lives and hurt families each day.

But now, there are efforts that would put millions of Americans' access to these advanced treatments at risk, and there is a very real threat to this Committee's ability to fund future increases in NIH to sustain its research efforts.

Republicans are, as we speak, rushing to dismantle the Affordable Care Act, which expanded health coverage to 20 million Americans, and ended restrictions on pre-existing conditions and lifetime caps that previously forced many of those with serious illnesses to choose between bankrupting their families, or foregoing treatment.

The deeply harmful House Republican Trumpcare bill would take us back to those bad days—meaning people across the country could lose access to the treatments that NIH research makes possible.

When I consider what that would mean, I think of one of my guests at the President's joint address, Marci Owens. Marci is from Seattle, and her mother died at age 27 after she became ill, then lost her job and the health insurance that came with it.

I'm deeply troubled that some Republicans want to return to a time when there were more stories like Marci's.

I recently heard from the wife of a father and self-employed contractor named Richard in my home State of Washington who, thanks to the ACA, had health insurance through Medicaid when he was diagnosed with an aggressive and rare form of leukemia.

His illness did not respond to conventional therapies, so his doctors with the Seattle Cancer Care Alliance enrolled him in a CAR–T-cell immunotherapy trial in a last ditch effort.

Richard is now in remission, with real hope for a long-term cure.

His family says the immunotherapy treatments saved his life. Absent the ACA, Richard's wife Jennifer believes she would now be raising their two children on her own.

I'm also concerned by the details of the President's budget that the Administration recently chose to make public. Cutting non-defense spending by $54 billion would require devastating cuts to the education, health and training programs our subcommittee funds.

And I don't see how NIH, which accounts for twenty percent of the funding in the bill, can avoid being affected.

I know members on both sides of the aisle agree on the importance of medical research—so this is not a partisan issue.

Just last December, Democrats and Republicans were able to come together to establish a new $4.8 billion funding stream for NIH in the CURES Act to help accelerate medical research efforts.

That was an important step forward—as was the bipartisan spending bill this subcommittee wrote last spring that would provide additional funding for NIH and other priorities in 2017.

Unfortunately, the fate of that spending bill is now uncertain.

Patients and families across the country are waiting and hoping for better cures and treatments, as well as for help with the other challenges they face, be it:
—finding quality child care,
—paying for college,
—or being able to get care when they are ill—and here in Congress, we should do our part to deliver.

Thank you, Mr. Chairman.

Senator BLUNT. Thank you, Senator Murray. We are always glad to have the chairman of the full committee with us. Senator Coch-

ran, thank you for being here today. Do you have any comments you would like to add?

STATEMENT OF SENATOR THAD COCHRAN

Senator COCHRAN. Mr. Chairman, thank you. I am pleased to see that we've empaneled some outstanding witnesses today to help us understand better the practical consequences of what we do here. And that includes appropriating dollars earmarked—excuse me—but earmarked for medical research. And I hope you won't disagree with our generosity.

Senator BLUNT. Thank you, Mr. Chairman. And I am pleased that we have the other members of the committee here and others will be coming.

We have great witnesses today. I am pleased to welcome them. Dr. Timothy Eberlein is the director of the Siteman Cancer Center in St. Louis, one of the largest cancer centers in the country. He's also Surgeon-in-Chief at Barnes-Jewish Hospital. Dr. Thomas Grabowski is the Director of the Memory and Brain Wellness Center and Alzheimer's Disease Research Center at the University of Washington. Dr. Stacy Schultz-Cherry is a member of the Department of Infectious Diseases at St. Jude's Research Hospital. And Dr. Jennifer Sasser is an assistant professor at the University of Mississippi Medical Center.

We look forward to your testimony.

Dr. Eberlein, we will start with you.

STATEMENT OF TIMOTHY J. EBERLEIN, M.D., DIRECTOR, ALVIN J. SITEMAN CANCER CENTER, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE IN ST. LOUIS, SURGEON–IN–CHIEF, BARNES–JEWISH HOSPITAL

Dr. EBERLEIN. Mr. Chairman and members of the subcommittee, thank you for the opportunity to appear before you to discuss how investments in biomedical research save lives every day through the development of new therapies and treatments. Thank you, Chairman Blunt, Chairman Cochran, and Ranking Member Murray, and the full subcommittee for your leadership in working to ensure that the Federal Government makes significant and sustained investments in biomedical research and for continuing to make NIH a priority in a challenging Federal judgment environment.

Our patients are seeing the benefits of Federal investments in research. Washington University was not only a member of the Human Genome Project, but we have used that expertise to pioneer the sequencing of cancer genomes. The ability to identify the genetic difference between healthy and cancerous tissues allowed us to apply this research to the clinical setting.

Today we are performing clinical trials that use state of the art genomic analysis to determine precision treatments in patients with leukemia, breast, lung, and other tumors. An additional strategy is to use genomic mutational analysis of an individual's cancer to treat many solid tumors, such as breast, brain, melanoma, lung, and head and neck cancers using a vaccine tailored to eradicate the patient's specific tumor with minimal side-effects and morbidity.

These clinical trials are examples that embody the goals of the Cancer Moonshot and the Precision Medicine Initiative, where we target treatments to the unique genetic characteristics of the patient and their disease.

In my own practice, I treat patients with breast cancer. Traditionally, we have operated on premenopausal patients who have early stage breast cancer and then treat them with radiation therapy and chemo therapy. But we know that approximately four out of five of these patients might be cured with surgery and radiation therapy alone.

The scientific challenge is that we don't yet know how to distinguish between the 20 percent who need additional chemotherapy from the 80 percent that don't. Can you imagine for a moment what that would mean for patients if we were able to make this determination—how patient's lives would improve, the cost of their care would decline if we avoided unnecessary therapy in four out of five of these cases? As we continue to develop our genomic understanding of cancer, I am confident we can get to a point where affordable personalized cancer treatments will be widely available.

Advances such as these are why we have been successful in reducing cancer mortality by 25 percent since 1991. And for children, an even more dramatic reduction of 66 percent between 1970 and 2014. The reduction in mortality, especially for children, is a direct result of improvements in treatment, treatments largely discovered through investigations made possible through grants from the NIH.

Sustained appropriations with increased funding to advance novel discoveries are responsible for the dramatic examples and improvement of life expectancy of patients with cancer in the United States. These investments have allowed us to understand the fundamental biology behind the disease and then to develop important strategies to develop therapies and cures.

What may be even more important, however, than the actual research, is the fact that virtually every scientist—whether in academia or industry—likely benefitted at some stage in their career by training at the National Institutes of Health like I did or through the utilization of NIH training grants and career development awards. This training equips scientists with the skills needed to develop 21st century cures and it represents an investment for which the country will reap benefits for decades to come.

Thank you for the opportunity to speak today and I look forward to answering any questions you may have.

[The statement follows:]

PREPARED STATEMENT OF TIMOTHY J. EBERLEIN, M.D.

Mr. Chairman and members of the subcommittee, thank you for the opportunity to appear before you to discuss how investments in biomedical research save lives every day through the development of new therapies and treatments.

My name is Timothy J. Eberlein. I am an actively practicing physician and also serve as the Chairman of the Department of Surgery at the School of Medicine at Washington University in St. Louis. I also serve as the Director of the Alvin J. Siteman Cancer Center.

Thank you, Chairman Blunt and Ranking Member Murray, for the opportunity to speak to the Subcommittee today, and for your leadership in working to ensure that the Federal Government makes a significant and sustained investment in biomedical research. I also want to thank the full Subcommittee for your work in providing substantial new resources for the National Institutes of Health and for continuing to make NIH a priority in a challenging Federal budget environment.

Our cancer center is a joint venture of Washington University and Barnes-Jewish Hospital in St. Louis, Missouri. We are the only NCI-designated comprehensive cancer center in the State of Missouri, and our 450 physicians and scientists care for over 50,000 cancer patients every year, patients who come to St. Louis from Missouri, surrounding States and across the Nation.

Our patients are seeing the benefits of Federal investments in research. Washington University was highly involved in the Human Genome Project, contributing roughly 25 percent of the final code. We have used that expertise to pioneer the sequencing of cancer genomes, allowing us to identify the genetic differences between healthy and cancerous tissues. As our scientific understanding has advanced, we have sought to apply this research to the clinical setting. One illustrative example involves Dr. Lukas Wartman, an oncologist and leukemia survivor, who experienced a second relapse of his disease while a fellow at Washington University. Researchers performed a detailed analysis of Lukas's cancer genome, and they found a gene which was expressing at a much higher level than normal. The research team then identified an existing drug typically used to treat kidney cancer, which targets tumors with this specific gene. Through this precision therapy, Dr. Wartman's disease went into remission, further enabling him to undergo a stem cell transplant. He now is working to care for cancer patients, and under his leadership, we have established a multidisciplinary Genomics Tumor Board that meets regularly to identify patients who might benefit from genome sequencing. Dr. Wartman embodies the idea behind the Cancer Moonshot and the Precision Medicine Initiative, where we target therapies and treatments to the unique genetic characteristics of the patient and their disease.

Utilizing sophisticated genomic analysis, we are on the cusp of fundamentally changing how we think about treating cancer by using targeted therapies that avoid unnecessary expensive treatments. By combining genomic mutational analysis of an individual's cancer, we are now doing clinical trials that treat many solid tumors such as breast, brain, melanoma, lung and head and neck cancers using a vaccine tailored to eradicate the patient's specific tumor with minimal side-effects and morbidity. Another opportunity comes through the use of nanoparticles to deliver therapies. Multiple myeloma is a cancer of the bone marrow that responds initially to chemotherapy, but the cancer usually recurs and becomes more resistant to treatment. We have had drugs that should eradicate the disease, but they tend to degrade once administered to the patient. Putting these drugs into nanoparticles, however, we are able to target the myeloma cancer cell, eradicating it with minimal side effects. Each of these novel clinical trials occurred at our cancer center funded through investigator-initiated research made possible by the NIH.

In my own practice, I treat patients with breast cancer. Traditionally, we have operated on pre-menopausal patients who have early stage breast cancer, and then treat them with radiation therapy and chemotherapy. However, we know that approximately four out of five of these patients might be cured with surgery and radiation therapy alone. The scientific challenge is that we do not yet know how to distinguish between the 20 percent who need the additional chemotherapy from the 80 percent who don't. Can you imagine for a moment, what that would mean to patients if we were able to make this determination—how their lives would improve if they were not subjected to the side-effects of chemotherapy? Can you imagine how the cost of their care would decline, if we avoided unnecessary therapy in four out of five of these cases? As we continue to develop our genomic understanding of cancer, I am confident we can get to the point where affordable personalized cancer treatments will be widely available but we need sustained, stable Federal support for research to get us there.

Another challenge I face in the operating room is being able to distinguish between cancerous and healthy tissue, and knowing exactly how much tissue to remove. Dr. Samuel Achilefu, a Washington University professor of radiology, has developed a set of goggles that help surgeons see and remove cancerous tumors as small as 1 mm in diameter, the thickness of about 10 sheets of paper. After a dye is injected into a patient's tumor, the cancerous cells "glow" when bathed in infrared light and viewed by the goggles. Dr. Achilefu's lab is also investigating phototherapy, killing cancer with light, through a new approach that utilizes already available radiopharmaceutical drugs that can create a light source within tumor cells. The light stimulates light-sensitive molecules that have been delivered to the cancer cells, converting them into highly toxic drugs. The advantage of this strategy is that it minimizes the impact on neighboring healthy tissue, which could lead to reduced side effects and better outcomes overall.

Advances such as these are why we have been successful in reducing cancer mortality by 25 percent since 1991.[1] The change in mortality in children has been even more dramatic, with the death rates among those aged birth to 19 having dropped 66 percent between 1970 and 2014.[2] I am particularly heartened by this progress with children. Adults have a greater ability to modify their behaviors that can lead to cancer—such as smoking or unhealthy diet. Children typically do not control the environment or the lifestyle decisions that can lead to their cancer. Thus, the reduction in mortality for children is a direct result of improvements in treatment-treatments largely discovered through investigations made possible through grants from the NIH.

Sustained appropriations with increased funding to advance novel discoveries and insights are responsible for the dramatic examples and improvement of life expectancy of patients with cancer in the United States. These investments have allowed us both to understand the fundamental biology behind disease and then to develop the strategies needed to develop therapies and cures. What may be even more important than the actual research, is the fact that virtually every scientist—whether in academia or industry—likely benefitted by training through the National Institutes of Health either by training in Bethesda, like I did, or through utilization of NIH training grants and/or career development grants. The reach of this funding in providing jobs and sustaining careers is monumental. But, even more critical, this training equips scientists with the skills needed to develop 21st Century cures. By equipping our Nation's best and brightest minds to tackle these incredibly difficult problems, we are making an investment for which the country will reap benefits for decades to come.

Thank you again for the opportunity to speak today, and I look forward to answering any questions you may have.

Senator BLUNT. Thank you, Dr. Eberlein. Dr. Grabowski.

STATEMENT OF THOMAS J. GRABOWSKI, JR., M.D. DIRECTOR, MEMORY AND BRAIN WELLNESS CENTER, ALZHEIMER'S DISEASE RESEARCH CENTER, INTEGRATED BRAIN IMAGING CENTER, UNIVERSITY OF WASHINGTON, SEATTLE

Dr. GRABOWSKI. Good morning, Chairman Blunt, Chairman Cochran, Ranking Member Murray, my Senator, and distinguished members of the subcommittee. Thank you for the opportunity to speak with you today about the value of medical research, something I do every day, and the pivotal role that NIH funding plays in our efforts to counter Alzheimer's disease.

My name is Tom Grabowski. I am a neurologist at the University of Washington, where I direct our clinical and research Center for Alzheimer's Disease and related memory disorders. My own research focuses on advanced brain imaging approaches in neurodegenerative disease.

Some five million Americans have Alzheimer's dementia, including one of nine people over age 65. Alzheimer's dementia has outsized emotional and material impacts on entire families. And it is the rare person whose circle has not been affected in some way by this disease. Alzheimer's is the only leading cause of death in 2017 that can't be cured, prevented, or even slowed. Consequently, increasing numbers of people are living and dying with Alzheimer's dementia, and the numbers are set to more than double and even triple by 2050.

Alzheimer's dementia is a relatively late consequence of a disease process that has gone on in the brain for 15 years or more. This long pre-symptomatic phase is our window of opportunity for intervention. The National Plan to Address Alzheimer's Disease that

[1] Siegel, R. L., K. Miller, A Jemal "Cancer Statistics, 2017." CA: A Cancer Journal for Clinicians. January/February 2017. p. 18.
[2] Ibid. p. 27.

guides our research efforts has an overarching first goal to prevent and effectively treat the disease by 2025. The way the math works out, if we could slow this disease down by 5 years out of those 15 pre-symptomatic years, we would cut Alzheimer's dementia in half, thus early stage biomarkers and early diagnosis toward early intervention are important priorities at our center and among our peer centers.

To really transform medicine for this disease, we must also transform the way we think about it. For example, unless we counter the stigma that is attached to Alzheimer's Disease, neither patients nor primary care givers are likely to cooperate with an agenda for early diagnosis.

At the University of Washington, we and our community partners have realized the importance of educating the public to understand the entire course of the disease, including its pre-symptomatic and mild cognitive impairment stages and the strengths a patient retains in the midst of it that become the basis for strength based interventions for persons with memory loss. Leading edge research really advances on this foundation of best care and community trust.

To accelerate progress, exciting new approaches are emerging. One example in our Center is reprogramming skin biopsy cells to make patient specific disease models available in the laboratory coupled with more knowledge of genetics and especially new gene editing technology, this could illuminate the different molecular pathways that drive Alzheimer's disease in different patients leading us toward a genuine precision medicine for Alzheimer's disease.

Better understanding of Alzheimer's disease ultimately requires more detailed data from each participant and aggregating that data nationally. Our field has a record of successful cooperation beginning with the NIH funded Alzheimer's Disease Centers Program that is operated for more than 30 years. I currently direct one of the Centers in this network that maintains subject registries and tissue repositories for Alzheimer's research and cross-institutional initiatives regularly leverage these resources. For example, the Alzheimer's Disease Neuroimaging Initiative, ADNI, has been pivotal to understanding early disease biomarkers and disease heterogeneity and has set a standard for data sharing and productivity.

As another example, the dominantly inherited Alzheimer's Disease Network has assembled a nationwide cohort of people known to be genetically susceptible to amyloid driven Alzheimer's disease and is now conducting one of the first precision medicine treatment trials for which UW is one of the performance sites.

We need more cooperation across NIH, industry, and charitable groups and new standards of data sharing. NIH funding is simply critical to all these efforts. It gives longevity to the research infrastructure, brings about standardization and thematic direction, enables cooperation at scale, trains new scientists, and ultimately is what will help us achieve the 2025 goal.

The Alzheimer's Accountability Act passed in the 2015 Omnibus Appropriations Bill authorized the NIH Director to analyze funding requirements beyond the NIH base budget to remain on track to achieve the goals of the National Plan. Dr. Collins has accordingly submitted a Professional Judgment Budget for fiscal year 2018 to

Congress. I urge the whole committee to support it with enthusiasm and with optimism. With this support, we can defeat this disease.

Thank you again for the opportunity to testify and I look forward to answering your questions.

[The statement follows:]

PREPARED STATEMENT OF THOMAS J. GRABOWSKI, JR., M.D.

Good morning, Chairman Blunt, Ranking Member Murray (my Senator), and distinguished Members of the Subcommittee. Thank you for the opportunity to testify today about the value of medical research, which is something I do every day. It is an honor to appear before your today to provide my view of the pivotal role NIH funding plays in our efforts to counter Alzheimer's disease, one of the central challenges in biomedicine.

My name is Thomas J. Grabowski, Jr. I am a neurologist at the University of Washington, where I direct our clinical and research Centers for Alzheimer Disease and other memory disorders, including the NIA-funded University of Washington Alzheimer Disease Research Center, and the UW Medicine Memory and Brain Wellness Center. My own research focuses on new brain imaging approaches in Alzheimer's disease and other degenerative diseases, using MRI imaging approaches.

Background

Some 5 million Americans have Alzheimer's dementia, including one in nine people over age 65. It is the rare person whose circle has not been touched by this disease. Alzheimer's dementia in a person has an outsized impact, emotional and material, on an entire family. Alzheimer's is the only leading cause of death that can't be cured, prevented, or even slowed in 2017. Consequently, increasing numbers of persons are living with Alzheimer's dementia, and dying from it, and the numbers are set to more than double and even triple by 2050.

If these facts aren't enough to call us to action, even larger numbers have latent pre-symptomatic disease. Alzheimer's dementia is a relatively late consequence of a disease process that has gone on in the brain for 15 years or more. The rate of outright dementia at age 65 is less than 1 percent, but by age 65 fully 20 percent of persons, despite normal memory, already have moderate to severe levels of amyloid plaques in the brain, as has been demonstrated by spinal fluid tests or amyloid PET brain scans.

Framing Alzheimer disease around its full course like this is critical to progress. The National Plan to Address Alzheimer's Disease has an overriding first goal to prevent and effectively treat Alzheimer's disease by 2025. The long pre-symptomatic phase is a window of opportunity for intervention. During this time period, different disease processes conspire to damage brain cells. Meanwhile positive lifestyle choices can postpone, literally by years, the tipping point at which the disease finally affects cognition. There is thus a clear opportunity for prevention of dementia by a combination of "precision medicine," brain health programs, and early intervention. If we can slow the disease process down by 5 years (out of those 15 pre-symptomatic years), we would cut Alzheimer's dementia in half. The search for a scalable imaging biomarker and early diagnosis and intervention are important priorities for our NIH-funded Alzheimer's Disease Research Center, and are goals shared by many of our peer Centers.

Toward Precision Medicine for Alzheimer's Disease

AD often is co-morbid with related chronic illnesses such as microvascular brain injury and Lewy body disease (LBD). Moreover, genetic risk for AD now clearly highlights the potential for multiple molecular drivers and perhaps multiple pathogenic pathways. The vision of the University of Washington (UW) AD Research Center (ADRC) is to bring individual clarity to this enormous complexity—to achieve precision medicine for AD so that the right person is treated at the right time with the right prevention or therapeutic.

Three key elements of precision medicine (Cholerton et al, 2016) are stratification by risk, detection of pathophysiological processes as early as possible (ideally before the disease manifests clinically), and alignment of mechanism of action of intervention(s) with an individual's molecular driver(s) of disease. Now gaining broad currency in cancer care, a precision medicine approach is beginning to be adapted to cognitive impairment and dementia.

Under NIH funding, and the leadership of Drs. George Martin, Murray Raskind, Thomas Montine, and most recently myself, the UW ADRC has been helping to de-

velop this approach to AD for 33 years. During its initial 20 years, our Center focused on AD genetic risk. Although we continue these efforts, the nature of AD genetics research has evolved and now is accomplished within large consortia rather than a single Center Project. Ten years ago, UW ADRC made 'Biomarkers and Experimental Therapeutics' our theme, recognizing that even the most sophisticated risk stratification will have limited impact without meaningful measures of preclinical disease and new therapeutics. The UW ADRC has been an incubator for development of recent national multicenter clinical trials, including the EXERT trial of aerobic exercise in Alzheimer disease (led by Dr. Laura Baker, now at Wake Forest University), a trial of Prazosin Treatment for Disruptive Agitation in Alzheimer's Disease (led by Drs. Elaine Peskind and Murray Raskind, UW), and the Study of Nasal Insulin to Fight Forgetfulness (SNIFF) led by Dr. Suzanna Craft, now at Wake Forest University.

Our current research projects advance our theme by pursuing fundamental research on mechanisms of aging and their intersection with Alzheimer disease pathogenesis, innovative development of novel therapeutics through protein design, and dynamic functional connectivity fMRI as a new window into pathophysiologic processes of preclinical AD. Our Center has been designed to create the knowledge and tools needed to advance pre-clinical biomarkers, to lay the groundwork for novel experimental therapeutics, to collaborate substantively in multicenter clinical trials, and to reach out to underrepresented populations.

UW ADRC vision and mission resonate strongly with the principles of the National Plan to Address Alzheimer's Disease. Ultimately, our efforts, combined with others, will drive optimally targeted and timed preventions and interventions for AD and related causes of dementia.

Overview of the University of Washington ADRC

The structure of our NIA-funded Alzheimer's Disease Research Center includes five Core resources, including a Clinical Core that characterizes and follows hundreds of research subjects; three formal research projects; and a Satellite Core that reaches out to American Indian and Alaskan native populations.

In research Project 1, ADRC Investigator Dr. Matthew Kaeberlein, also the Co-Director of the Nathan Shock Center on Basic Biology of Aging (funded by NIA), investigates the mechanisms by which two important and highly conserved signaling pathways involved in cellular aging determine cellular resistance to amyloid beta toxicity, using a roundworm animal model. The Project aims for fundamental insights into the conserved cellular responses to amyloid beta and the identification of new therapeutic targets in Alzheimer's disease.

In Project 2, ADRC Investigator Dr. David Baker, also the Director of the UW Institute for Protein Design, is designing small molecules that bind specifically to different forms of amyloid beta (such as soluble monomers) using the Rosetta software suite for rational protein design, coupled with a distinctive crowdsourcing approach that his laboratory has used to great success in HIV and influenza. The idea is that rational protein design will enable evaluation of therapeutic approaches that target different hypotheses as to the precise mechanism of amyloid toxicity.

In Project 3, ADRC Investigator Dr. Thomas Grabowski, also the Director of the UW Integrated Brain Imaging Center (which has received major funding from NINDS), is investigating new functional MRI imaging approaches for preclinical detection of Alzheimer disease. Functional connectivity fMRI (fcMRI) can map brain networks based on detecting synchronized activity across separate brain regions. In particular, the brains "default network" is systematically affected in early Alzheimer disease. In this project, fcMRI measures of default network integrity are being validated against CSF protein markers of Alzheimer's disease, extending our Alzheimer's Disease Research Center's work on preclinical biomarkers.

Therapeutic Pipeline Project (TPP). In 2015 the Ellison Foundation made a $6 million gift to UW Medicine to foster the development of a "therapeutic pipeline" for AD, based on precision medicine principles. This project leverages our Center's NIH-funded resources, and includes next-generation whole-exome sequencing to stratify trial-ready subject groups, and the use of induced pluripotent stem cells to develop subject-specific neuron cultures that can be used as disease models to understand the different molecular pathways that drive Alzheimer disease in different individuals. We are turning to these tools to investigate Alzheimer disease mechanisms that include mTOR aging pathway, immune inflammatory responses by microglia, and endosomal trafficking of amyloid beta.

Our Satellite Core is led by Dr. Dedra Buchwald of Washington State University, also the Director of Parterships for Native Health. Drawing on the vast experience of Dr. Buchwald's group in carrying out research in this unique, underserved, and complex population, the Satellite Core will follow 450 aging reservation-dwelling

American Indians at three sites in Oklahoma, Arizona, and South Dakota for progression of cognitive impairment and imaging markers of neurodegenerative disease.

Besides the Washington-based Centers mentioned above, the UW ADRC is closely partnered with the Adult Changes in Thought study, a longitudinal population-based prospective cohort study of brain aging and incident dementia in the Seattle metropolitan area, based at the Group Health Cooperative in Seattle, directed by Drs. Eric Larsen and Paul Crane, and continuously funded by the National Institute on Aging for 28 years.

On a Foundation of Care and Community Trust

Our ADRC is partnered with the UW Medicine Memory and Brain Wellness Center clinic, a comprehensive multidisciplinary evaluation and treatment service for disorders affecting memory and cognition. Our combined mission is to promote the well-being of persons living with memory loss and their families, by providing exceptional care, advancing scientific understanding, and building dementia-friendly communities. The themes of the Memory and Brain Wellness Center clinic are early and accurate diagnosis, strengths-based reframing and treatment, and community transformation. Patients have access to state of the art genetic and imaging studies, integrated mental healthcare, cognitive rehabilitation, educational programming, and the option to participate in research via our patient Registry, through which they may connect to the ADRC, clinical trials, brain health studies, and others.

For most people, even medical providers, ideas about Alzheimer disease are framed around dementia. To really transform medicine for Alzheimer's disease, we must also transform the way we (patients and families, physicians, and our society) think about the disease. For example, unless we counter the stigma attached to Alzheimer disease, neither patients nor primary care physicians are likely to cooperate with the important agenda of early detection. At the University of Washington, we and our community partners have realized the importance of educating the public to understand the entire course of Alzheimer disease, including its pre-symptomatic and mild cognitive impairment stages, and the strengths a person retains in the midst of it, as well as the importance of strengths-based programs for persons with memory loss.

Our Washington State community partners include Momentia, a grassroots social movement in Seattle of persons living with early stage memory loss, transforming what it means to live with memory loss through empowerment and engagement in the community; the Western and Central Washington State Chapter of the Alzheimer's Association; the Dementia Action Collaborative implementing the Washington State Plan to Address Alzheimer's Disease; and other groups providing advocacy or engagement programming.

We envision a world in which people live well with memory loss and can rely upon the best care, within a community of support. Leading-edge research really advances on a foundation of best care and community trust.

Critical Importance of NIH Funding

Progress in understanding of AD ultimately requires more detailed data from each research participant, and aggregating these data nationally. Our field has a record of successful large-scale cooperation, beginning with the Alzheimer's Disease Centers program of the National Institute on Aging that has operated for more than 30 years. Ours is one such Center in this network, which forms the backbone, and maintains subject registries and tissue repositories for American AD research. Cross-institutional initiatives regularly leverage these resources. For example, the NIH-funded Alzheimer's Disease Sequencing Project (funded by NIA and the National Human Genome Research Institute) and Dominantly inherited Alzheimer Disease Network (DIAN, funded by NIA) make use of our resources. The Alzheimer Disease Neuroimaging Initiative has been pivotal to understanding early disease biomarkers and disease heterogeneity, and has set a standard for data sharing and productivity, continued and extended by other open neuroscientific initiatives from NIH (e.g. the Human Connectome Project) and charitable sources (e.g. the Allen Institute for Brain Science and Sage Bionetworks, both in Seattle). NIH- and industry-sponsored treatment trials also make use of the resources of the Alzheimer Disease Centers. At our Center, these have included the DIAN Trials Unit, the Biogen EMERGE study of Aducanamab, and the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) study (funded by NIA and a public-private consortium).

NIH funding is simply critical to all these efforts. It underlies most of the effort I have outlined in my testimony. NIH funding is what gives longevity to the research infrastructure, brings about standardization and thematic direction, enables cooperation at scale, trains new scientists, and ultimately will achieve the 2025 goal.

We need to bring about even more cooperation across NIH, industry, and charitable groups; and new standards of data sharing to promote progress.

The Alzheimer's Accountability Act authorized the NIH Director to analyze research funding requirements, beyond the NIH base budget, to remain on track to achieve the goals of the National Plan, with specific, targeted milestones Dr. Collins has submitted a Professional Judgment Budget for fiscal year 2018. I urge it on you with enthusiasm, and with optimism that we can defeat this disease.

Resources

UW Medicine Memory and Brain Wellness Center: http://www.depts.washington.edu/MBWC.

Living with Memory Loss: http://depts.washington.edu/mbwc/content/page-files/LWML-Handbook__reduced__2__27__17.pdf.

UW Alzheimer's Disease Research Center: http://www.pathology.washington.edu/research/adrc.

Momentia: http://www.momentiaseattle.org.

Precision Medicine for Alzheimer's Disease: Cholerton B, Larson EB, Quinn JF, Zabetian CP, Mata IF, Keene CD, Flanagan M, Crane PK, Grabowski TJ, Montine KS, Montine TJ. Precision Medicine: Clarity for the Complexity of Dementia. Am J Pathol 186:500–6, 2016.

Precision Medicine: Clarity for the Complexity of Dementia. [The article follows:]

The American Journal of Pathology, Vol. 186, No. 3, March 2016

ELSEVIER

Neuropathology Theme Issue

The American Journal of PATHOLOGY

ajp.amjpathol.org

REVIEW

Precision Medicine

Clarity for the Complexity of Dementia

Brenna Cholerton,* Eric B. Larson,† Joseph F. Quinn,†§ Cyrus P. Zabetian,¶‖** Ignacio F. Mata,¶** C. Dirk Keene,†† Margaret Flanagan,†† Paul K. Crane,‡‡ Thomas J. Grabowski,**§§ Kathleen S. Montine,†† and Thomas J. Montine††

From the Departments of Psychiatry and Behavioral Sciences, Neurology,** Pathology,†† Medicine,‡‡ and Radiology,§§ University of Washington, Seattle, Washington; the Group Health Research Institute,† Seattle, Washington; the Department of Neurology,‡ Oregon Health and Science University, Portland, Oregon; the Portland Veterans Affairs Medical Center,§ Portland, Oregon; and the Geriatric Research, Education, and Clinical Center¶ and the Parkinson's Disease Research, Education, and Clinical Center,‖ VA Puget Sound Health Care System, Seattle, Washington*

Accepted for publication December 3, 2015.

Address correspondence to Thomas J. Montine, M.D., Ph.D., Department of Pathology, University of Washington, Box 357470, Seattle, WA 98195. E-mail: tmontine@uw.edu.

Three key elements to precision medicine are stratification by risk, detection of pathophysiological processes as early as possible (even before clinical presentation), and alignment of mechanism of action of intervention(s) with an individual's molecular driver(s) of disease. Used for decades in the management of some rare diseases and now gaining broad currency in cancer care, a precision medicine approach is beginning to be adapted to cognitive impairment and dementia. This review focuses on the application of precision medicine to address the clinical and biological complexity of two common neurodegenerative causes of dementia: Alzheimer disease and Parkinson disease. *(Am J Pathol 2016, 186: 500–506; http://dx.doi.org/10.1016/j.ajpath.2015.12.001)*

The goal of precision medicine is to harness new knowledge and technology to optimize the timing and targeting of interventions for maximal therapeutic benefit. There are three key elements to precision medicine: stratification by risk, detection of pathophysiological processes as early as possible and preferably before clinical presentation, and alignment of mechanism of action of intervention(s) with an individual's molecular driver(s) of disease.[1] Ideally, precision medicine contrasts with the traditional approach in graded surveillance on the basis of level of risk, and intervention to suppress pathophysiologic processes while still latent (Figure 1). The approach of precision medicine, applied for decades to rare diseases like phenylketonuria and, more recently, to cystic fibrosis,[2] now has broad currency in cancer care and is the focus of a recent White House initiative to transform medical practice (Precision Medicine Cohort Program, *https://www.nih.gov/research-training/precision-medicine-initiative*, last accessed December 3, 2015). Herein, we review how the key elements of precision medicine are beginning to bring clarity to the clinical and biological complexity of dementia.

Clinical Complexity

Dementia is a major public health threat that causes untold suffering to patients and caregivers, and is poised to overwhelm health care systems in the coming decades.[3,4] Population- or community-based studies of brain aging and incident dementia from around the world have repeatedly identified three common pathological correlates of dementia. These include Alzheimer disease (AD) neuropathologic changes, including senile plaques (SPs) and neurofibrillary tangles (NFTs); vascular brain injury (VBI), especially caused by small-vessel disease; and Lewy body disease (LBD; *vide infra*), with recognition that other neuropathologic changes, including cerebral

Supported by NIH grants P50 AG005136 (T.J.M., C.D.K., T.J.G.), P50 NS062684 (T.J.M., C.P.Z., J.F.Q., T.J.G.), R01 AG042437 (P.K.C.), R01 NS065070 (C.P.Z.), and U01 AG006781 (E.B.L.); the Office of Research and Development Medical Research Service, Department of Veterans Affairs (C.P.Z., J.F.Q.); and the Nancy and Buster Alvord Endowment (T.J.M.).

Disclosures: None declared.

This article is part of a review series on neuropathology.

http://dx.doi.org/10.1016/j.ajpath.2015.12.001

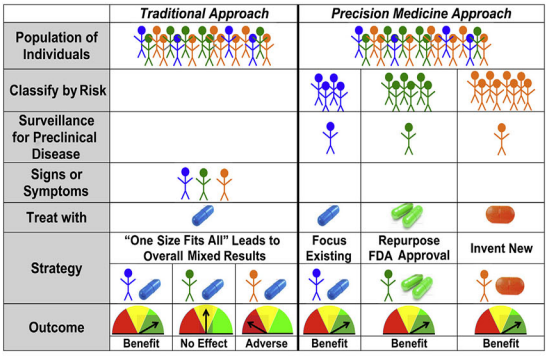

Figure 1 Schematic of traditional and precision medicine approaches. Key elements of precision medicine are classification by risk, surveillance for preclinical disease, and alignment of an expanding repertoire of treatments with the molecular drivers of disease.

amyloid angiopathy and hippocampal sclerosis, are found in older adults and associated with cognitive impairment.[5–12] In the Seattle-based Adult Changes in Thought study, a population-based study of brain aging and incident dementia in individuals 65 years or older, the population attributable risk for dementia from these diseases is 45% for AD, 33% for VBI, and 10% for LBD.[13]

In a collaborative study that pooled data from 1672 brain autopsies from multiple population- and community-based studies, the most common neuropathologic finding was some combination of these diseases, leaving open the extent to which each disease may have contributed to cognitive decline.[5] More important, 424 cognitively nonimpaired individuals in the same research studies, who died proximate to extensive neuropsychological evaluation, also showed neuropathologic evidence for the same diseases but at generally lower levels, although some individuals died with advanced neuropathologic changes despite relatively preserved function. Figure 2 presents updated results from 405 brain autopsies from the Adult Changes in Thought study as of December 2014, following exactly the same approach as our earlier publication.[5] Results are separated by cognitive status into high cognitive performers (Figure 2A), low cognitive performers (Figure 2B), early dementia (Figure 2C), and late dementia (Figure 2D). Figure 2E shows average values for each group. The proportion of individuals with any pathological evidence of the two neurodegenerative diseases did not change substantially across the four groups; AD pathological change was present in 97% to 100%, and LBD was present in 12% to 20%. The proportion of individuals with VBI ranged from 32% in high cognitive performers to 64% in late dementia. These results from a typical US urban and suburban population demonstrate that the aging brain is a complex environment in which AD, VBI, and LBD each have a latent phase, are variably mixed in older patients with and without dementia, and the overall burden of disease(s) increases in severity with increasing cognitive impairment.

LBD is especially complex because this pathological change is associated with clinical diagnoses of dementia with Lewy bodies (DLB) or Parkinson disease (PD) with or without mild cognitive impairment (PD-MCI) or dementia (PDD).[14–16] DLB most commonly is associated with a combination of the pathological features of AD and LBD, and less commonly with widespread LBD in the absence of AD neuropathologic changes.[17,18] Although recognized as a disorder of motor control and characterized by brainstem Lewy bodies (LBs), PD also is accompanied by cognitive impairment or dementia in a large fraction of patients, approximately one-quarter even at the time of initial diagnosis.[19–25] Results from the Pacific Northwest Udall Center widely replicate the experience of research cohorts from around the globe showing that MCI and dementia are common in PD.[26] Indeed, approximately 80% of the initial 603 research volunteers to the Pacific Northwest Udall Center with PD also were diagnosed with MCI or dementia on intake evaluation, although, admittedly, this estimate from a research cohort may be higher than in community settings. Figure 3 shows basic characteristics of these 491 individuals with PD-MCI or PDD. MCI and dementia occurred much more commonly with shorter duration of PD in older individuals, and more commonly with longer disease duration in younger individuals (Fischer's exact test, $P < 0.0001$).[26] The pathological bases of PDD, and its distinction from DLB, remain unclear. Hence, the extent to which the pathophysiologic processes that lead to brain regional SP, NFT, or LB formation contribute to cognitive impairment and dementia in an individual with DLB, PD-MCI, or PDD remains impossible to determine. Increased knowledge of molecular drivers and accurate biomarkers of pathophysiologic processes from advances in precision medicine will help bring greater clarity to this complex clinical situation.

Biological Complexity

On the basis of abundant genetic, experimental, pathologic, and biomarker data, two key molecular drivers of AD

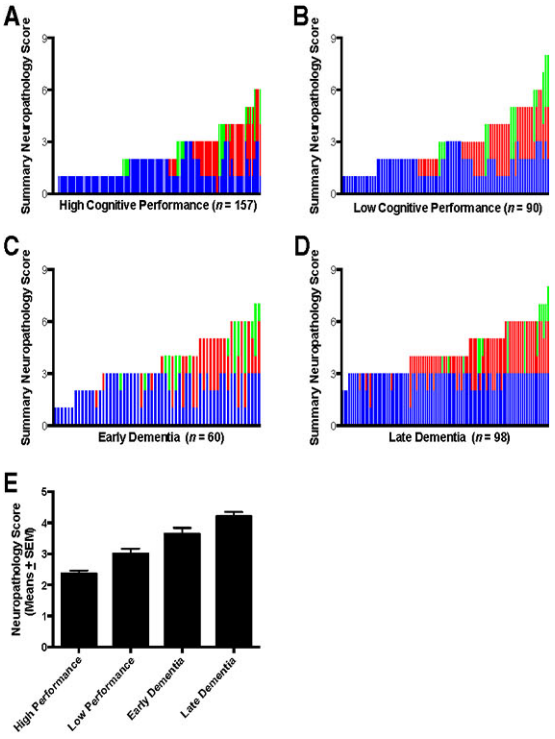

Figure 2 Results from 408 brain autopsies in the Adult Changes in Thought (ACT) study as of December 2014. Three cases of dementia were excluded that had neuropathologic diagnosis of frontotemporal lobar degeneration, traumatic brain injury, or extensive laminar necrosis. Summary neuropathology scores for Alzheimer disease (AD; blue bars), vascular brain injury (VBI; red bars), and Lewy body disease (LBD; green bars) for the remaining 405 cases were determined using consensus neuropathologic evaluations, as described previously,[5] and then plotted for each individual stratified by cognitive performance (**A**–**D**) or summarized for each cognitive performance group (**E**). Cognitive performance was determined using the Cognitive Assessment Screening Instrument (CASI), and dementia was diagnosed according to Diagnostic Statistical Manual-IVR criteria. CASI scores ≥91 are in the upper four quintiles of the ACT cohort. The individuals (means ± SD age, M:F ratio) with i) CASI ≥ 91 at last evaluation within 2 years of death are the High Cognitive Performance group (85 ± 7 years, 73:85; **A** and **E**); ii) CASI <91 but not diagnosed with dementia at last evaluation within 2 years of death are the Low Cognitive Performance group (87 ± 6 years, 46:44; **B** and **E**); iii) dementia at last evaluation within 2 years of death are the Early Dementia group (89 ± 6 years, 26:34; **C** and **E**), and iv) dementia at last evaluation >2 years before death are the Late Dementia group (91 ± 6 years, 37:61; **D** and **E**). One-way analysis of variance for the data presented in **E** has $P < 0.0001$ and Bonferroni-corrected $P < 0.05$ for all possible paired comparisons.

appear to be $A\beta_{42}$ and pathological forms of tau.[27] We quantified $A\beta_{42}$ and paired helical filament (PHF)-tau in the cerebral cortex from 325 consecutive Adult Changes in Thought participants and observed a generally positive, but complex, relationship.[28] Given the comprehensiveness of brain autopsy, herein, we reanalyzed these published data[28] to test whether isolating AD from common comorbid conditions might bring greater clarity to the quantitative relationship between cerebral cortical $A\beta_{42}$ and PHF-tauamong individuals without dementia who were last evaluated within 2 years of death (Figure 4). Indeed, exclusion of cases with LBD or VBI and focusing on those whose *APOE* genotype varied by only one allele revealed a strong positive correlation between cerebral cortical concentrations of $A\beta_{42}$ and PHF-tau in temporal lobe that approximated a line ($P < 0.0001$). In contrast, cerebral cortical concentrations of $A\beta_{42}$ and PHF-tau were weakly correlated in the frontal lobe ($P < 0.05$). The concentration of $A\beta_{42}$ was strongly related to *APOE* genotype regardless of cerebral cortical region, whereas the concentration of PHF-tau was significantly related to *APOE* genotype only in the temporal, and not in the frontal, lobe. These novel results provide insight into the molecular underpinnings of AD, and will help guide molecular neuroimagers as they now are beginning to compare results of imaging ligands for cerebral amyloid and pathological tau.

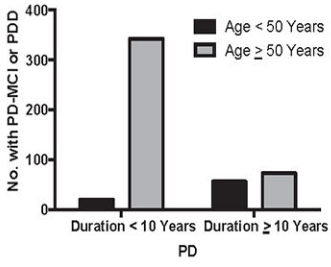

Figure 3 Stratification by age of Parkinson disease (PD) onset and duration of PD for the 491 individuals who volunteered to join the Pacific Northwest Udall Center (PANUC). Data are the number of PANUC participants diagnosed as PD with mild cognitive impairment (PD-MCI) or PD with dementia (PDD) at their initial evaluation of a total cohort of 619 individuals with PD.

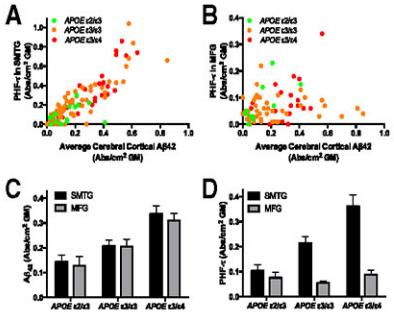

Figure 4 Quantification of $A\beta_{42}$ and paired helical filament (PHF)-tau in superior and middle temporal gyri (SMTG) or middle frontal gyrus (MFG) from Adult Changes in Thought study brain autopsies.[28] All participants were last evaluated within 2 years of death when they were diagnosed as not meeting criteria for dementia. Cases with neuropathologic changes other than Alzheimer disease were excluded, and we limited our analysis to only those with genotypes *APOE* ε2/ε3, *APOE* ε3/ε3, or *APOE* ε3/ε4. Molecular concentrations were obtained using a method called Histelide (histology and ELISA on a glass slide)[29] and expressed in units of absorbance (Abs) at 405 nm normalized to gray matter (GM) area. Concentrations of $A\beta_{42}$ did not vary significantly across the two regions (**C**) and were averaged into a single value for cerebral cortex in correlation analyses. **A** and **B** plot average cerebral cortical $A\beta_{42}$ versus PHF-tau concentrations in SMTG or MFG. There is a highly statistically significant correlation between $A\beta_{42}$ and PHF-tau concentrations in SMTG ($P < 0.0001$), and a much weaker correlation in MFG ($P < 0.05$). **C** and **D** plot average concentration of $A\beta_{42}$ or PHF-tau concentration in SMTG and MFG stratified by *APOE* genotype. Two-way analysis of variance for $A\beta_{42}$ concentration had $P < 0.0001$ for *APOE* genotype, but was not significant for region or interaction. Two-way analysis of variance for PHF-tau concentration in SMTG had $P < 0.01$ for *APOE* genotype, $P < 0.0001$ for region, and $P < 0.01$ for interaction. Tukey's multiple comparisons test for PHF-tau concentration showed $P < 0.01$ for all pair-wise comparisons of *APOE* genotypes in SMTG but no significant difference among *APOE* genotypes in MFG. $n = 105$ (**A** and **B**, SMTG); $n = 77$ (**A** and **B**, MFG).

One approach to identification of additional molecular drivers of disease is determining disease risk. Comprehensive risk assessment requires evaluation of environment, lifestyle, and inherited risk; herein, we focus on recent advances in understanding inherited risk. Recent genome-wide association studies have linked genetic variants across the human genome with a clinical diagnosis of AD dementia. In 2013, the International Genomics of Alzheimer's Project reported results from >74,000 individuals that brought to 21 the total number of genetic susceptibility loci for a clinical diagnosis of AD dementia,[30] and more have been discovered since.[31,32] It is important to recognize that these genomic studies have linked genetic variants with the clinical diagnosis of AD dementia. Recognizing that the clinical expression of AD dementia is the culmination of stress and injury, response to injury, consumption of reserve, and compensation, we sought to clarify the mechanisms underlying genetic susceptibility for AD dementia by determining their association with SPs and NFTs. As part of a large multisite collaboration, we assembled neuropathologic data from 4914 brain autopsies, largely from research cohorts, and performed a genome-wide association study as well as analysis of the then known 21 International Genomics of Alzheimer's Project genetic risk loci for AD dementia.[30] Genome-wide significance was observed for the following: i) neuritic plaques (a subset of SPs that had been assessed in all cases), NFTs, cerebral amyloid angiopathy, and LBD, with several variants in and around the apolipoprotein E gene (*APOE*); ii) neuritic plaques with GalNAc transferase 7 gene (*GALNT7*), ATP-binding cassette, subfamily G, member 1 gene (*ABCG1*), and an intergenic region on chromosome 9; and iii) hippocampal sclerosis with potassium large conductance calcium-activated channel, subfamily M, β member 2 (*KCNMB2*). Of the 21 International Genomics of Alzheimer's Project genetic risk loci for clinically defined AD dementia, 12 were confirmed in our smaller clinicopathologic sample: *CR1*, *BIN1*, *CLU*, *MS4A6A*, *PICALM*, *ABCA7*, *CD33*, *PTK2B*, *SORL1*, *MEF2C*, *ZCWPW1*, and *CASS4*. Of these 12 loci, 9 showed a larger odds ratio in the clinicopathologic sample than in the clinical sample. As anticipated, comparison of effect sizes for risk of AD dementia (function) with effect size for NFTs or neuritic plaques (structure) showed a significant positive correlation. Although limited by relatively low sample size and design characteristics, such that only data from people with late-onset AD dementia and cognitively normal elderly controls were considered, the same approach showed no association with comorbid LBD and perhaps ominously showed a moderate negative correlation with comorbid VBI.

Like AD dementia, large consortia have pursued genetic variants associated with PD (defined by motor symptoms) using genomic approaches and have identified a similar number of risk loci.[33,34] Furthermore, autopsy-based genome-wide association studies for PD also have contributed to novel insights into the genetic risk architecture for PD.[35] The Pacific Northwest Udall Center has organized the PD Cognitive Genetics Consortium to investigate the genetic risk for dementia in the context of PD. Initially using a candidate gene approach, this multisite collaborative effort has built on knowledge gained from prior case-control studies and identified genetic variants that increase risk for

Table 1 Risk from Candidate Genes for PD When Compared with Unaffected Individuals, or for PDD When Compared with Nondemented Individuals with PD

Candidate gene	PD risk	PDD risk
SNCA	↑	—
MAPT	↑	—
APOE ε4	—	↑
GBA	↑	↑
LRRK2	↑	↓

—, no significant association; ↑, statistically increased risk; ↓, statistically decreased risk; PD, Parkinson disease; PDD, PD with dementia.

PD motor symptoms and PDD together, PD motor symptoms alone, and PDD alone (Table 1).[36–38] Current efforts by the PD Cognitive Genetics Consortium are using genomic approaches to accelerate discovery of novel genetic susceptibility loci for cognitive impairment in PD.

Precision Medicine

In precision medicine, because greater knowledge about genetic risk fuels development of interventions tailored to specific molecular drivers, there will be growing need for the third component, detection of pathophysiologic processes as early as possible, ideally during latency. There has been strong progress in this area of research, with many groups around the world pursuing a variety of technologies. Notable successes in AD are positron emission tomography imaging for cerebral amyloid[39] and, more recently, pathological tau,[40] and cerebrospinal fluid concentrations of $A\beta_{42}$ (a major component of SPs) and tau species (a major component of NFTs).[41–45] Although early, experience with imaging of pathological tau suggests that the regional distribution may be critically important, a possibility reinforced by our quantification of PHF-tau. A similar approach and outcomes have been achieved in PD with neuroimaging and measurement of cerebrospinal fluid biomarkers.[45–50] Interestingly, cerebrospinal fluid α-synuclein concentration (a major component of LB) may not only aid in diagnosis of LBD, but also improve the diagnostic accuracy of AD biomarkers.[51] Molecular neuroimaging for pathological α-synuclein is a high priority for development.[52]

Although envisioned primarily as diagnostic aides or potential surrogates for pharmacological activity,[53] results suggest that biomarkers may also serve to group patients by underlying pathophysiologic processes that apparently can cross classic diagnostic boundaries. From this perspective, neuroimaging and biofluid biomarkers might, in the future, serve as evidence for selection of therapeutics in addition to assignment to a clinical diagnostic category.

Success in precision medicine for diseases that cause dementia will require much more work to fill gaps in our knowledge regarding risk stratification, surveillance for preclinical pathophysiologic processes, and development of new interventions that are tailored to key molecular drivers of disease. Of these, we are having the most success in identifying genetic risk and developing tools to detect pathophysiologic processes; major advances in the repertoire of disease-modifying therapies are needed. Despite our incomplete knowledge, several groups are now beginning to incorporate the approach of precision medicine into clinical trials for AD and PD. Indeed, determination of genetic risk as a partial window into molecular drivers of disease, coupled with neuroimaging and biomarkers of underlying pathophysiologic processes, has been incorporated into the design of several clinical trials. These include the Dominantly Inherited Alzheimer Network Trials Unit,[54] the Alzheimer's Prevention Initiative,[55] and Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease[56] trial, which all focus on subgroups of individuals with known genetic risk for AD, and biofluid biomarkers or neuroimaging to detect onset of disease. In addition, major research initiatives are underway to advance therapeutics that oppose the functional outcomes of mutations in *LRRK2* or *GBA* that increase risk of PD. We expect this is only the beginning for a precision medicine approach to clinical and biological complexity of AD and PD.

References

1. Montine TJ, Montine KS: Precision medicine: clarity for the clinical and biological complexity of Alzheimer's and Parkinson's diseases. J Exp Med 2015, 212:601–605
2. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, Colombo C, Davies JC, De Boeck K, Flume PA, Konstan MW, McColley SA, McCoy K, McKone EF, Munck A, Ratjen F, Rowe SM, Waltz D, Boyle MP: Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 2015, 373:220–231
3. Global Burden of Disease Study 2013 Collaborators: Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015, 386:743–800
4. GBD 2013 Mortality and Causes of Death Collaborators: Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015, 385: 117–171
5. Sonnen JA, Santa Cruz K, Hemmy LS, Woltjer R, Leverenz JB, Montine KS, Jack CR, Kaye J, Lim K, Larson EB, White L, Montine TJ: Ecology of the aging human brain. Arch Neurol 2011, 68:1049–1056
6. Sonnen JA, Larson EB, Haneuse S, Woltjer R, Li G, Crane PK, Craft S, Montine TJ: Neuropathology in the adult changes in thought study: a review. J Alzheimers Dis 2009, 18:703–711
7. Haroutunian V, Serby M, Purohit DP, Perl DP, Marin D, Lantz M, Mohs RC, Davis KL: Contribution of Lewy body inclusions to dementia in patients with and without Alzheimer disease neuropathological conditions. Arch Neurol 2000, 57:1145–1150
8. EClipSE Collaborative Members: Cohort profile: epidemiological clinicopathological studies in Europe (EClipSE). J Alzheimers Dis 2009, 18:659–663
9. Brayne C, Richardson K, Matthews FE, Fleming J, Hunter S, Xuereb JH, Paykel E, Mukaetova-Ladinska EB, Huppert FA, O'Sullivan A, Dening T: Neuropathological correlates of dementia in over-80-year-old brain donors from the population-based Cambridge city over-75s cohort (CC75C) study. J Alzheimers Dis 2009, 18: 645–658
10. O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L, Crain BJ, Pletnikova O, Rudow G, Iacono D, Riudavets MA, Driscoll I, Price DL, Martin LJ, Troncoso JC: Neuropathologic studies of the Baltimore Longitudinal Study of Aging (BLSA). J Alzheimers Dis 2009, 18:665–675
11. Yu L, Boyle PA, Leurgans S, Schneider JA, Kryscio RJ, Wilson RS, Bennett DA: Effect of common neuropathologies on progression of late life cognitive impairment. Neurobiol Aging 2015, 36:2225–2231
12. Nelson PT, Abner EL, Schmitt FA, Kryscio RJ, Jicha GA, Smith CD, Davis DG, Poduska JW, Patel E, Mendiondo MS, Markesbery WR: Modeling the association between 43 different clinical and

pathological variables and the severity of cognitive impairment in a large autopsy cohort of elderly persons. Brain Pathol 2010, 20:66–79

13. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, Craft S, Leverenz JB, Montine TJ: Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol 2007, 62:406–413
14. Montine TJ, Koroshetz WJ, Babcock D, Dickson DW, Galpern WR, Glymour MM, Greenberg SM, Hutton ML, Knopman DS, Kuzmichev AN, Manly JJ, Marder KS, Miller BL, Phelps CH, Seeley WW, Sieber BA, Silverberg NB, Sutherland M, Torborg CL, Waddy SP, Zlokovic BV, Corriveau RA: Recommendations of the Alzheimer's disease-related dementias conference. Neurology 2014, 83:851–860
15. Geurtsen GJ, Hoogland J, Goldman JG, Schmand BA, Troster AI, Burn DJ, Litvan I: Parkinson's disease mild cognitive impairment: application and validation of the criteria. J Parkinsons Dis 2014, 4: 131–137
16. Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, Brooks DJ, Dickson DW, Dubois B, Emre M, Fahn S, Farmer JM, Galasko D, Galvin JE, Goetz CG, Growdon JH, Gwinn-Hardy KA, Hardy J, Heutink P, Iwatsubo T, Kosaka K, Lee VM, Leverenz JB, Masliah E, McKeith IG, Nussbaum RL, Olanow CW, Ravina BM, Singleton AB, Tanner CM, Trojanowski JQ, Wszolek ZK: DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. Neurology 2007, 68:812–819
17. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, Montine TJ: National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 2012, 8: 1–13
18. Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Trojanowski JQ, Vinters HV, Hyman BT: National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol 2012, 123:1–11
19. Stefanova E, Ziropadja L, Stojkovic T, Stankovic I, Tomic A, Jecmenica-Lukic M, Petrovic I, Kostic V: Mild cognitive impairment in early Parkinson's disease using the Movement Disorder Society Task Force criteria: cross-sectional study in Hoehn and Yahr stage 1. Dement Geriatr Cogn Disord 2015, 40:199–209
20. Mayeux R, Denaro J, Hemenegildo N, Marder K, Tang MX, Cote LJ, Stern Y: A population-based investigation of Parkinson's disease with and without dementia: relationship to age and gender. Arch Neurol 1992, 49:492–497
21. Aarsland D, Tandberg E, Larsen JP, Cummings JL: Frequency of dementia in Parkinson disease. Arch Neurol 1996, 53:538–542
22. Hobson P, Meara J: Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. Mov Disord 2004, 19:1043–1049
23. Buter TC, van den Hout A, Matthews FE, Larsen JP, Brayne C, Aarsland D: Dementia and survival in Parkinson disease: a 12-year population study. Neurology 2008, 70:1017–1022
24. Domellof ME, Ekman U, Forsgren L, Elgh E: Cognitive function in the early phase of Parkinson's disease, a five-year follow-up. Acta Neurol Scand 2015, 132:79–88
25. Hobson P, Meara J: Mild cognitive impairment in Parkinson's disease and its progression onto dementia: a 16-year outcome evaluation of the Denbighshire cohort. Int J Geriatr Psychiatry 2015, 30: 1048–1055
26. Cholerton BA, Zabetian CP, Quinn JF, Chung KA, Peterson A, Espay AJ, Revilla FJ, Devoto J, Watson GS, Hu SC, Edwards KL, Montine TJ, Leverenz JB: Pacific Northwest Udall Center of excellence clinical consortium: study design and baseline cohort characteristics. J Parkinsons Dis 2013, 3:205–214
27. Raskin J, Cummings J, Hardy J, Schuh K, Dean RA: Neurobiology of Alzheimer's disease: integrated molecular, physiological, anatomical, biomarker, and cognitive dimensions. Curr Alzheimer Res 2015, 12: 712–722
28. Postupna N, Keene CD, Crane PK, Gonzalez-Cuyar LF, Sonnen JA, Hewitt J, Rice S, Howard K, Montine KS, Larson EB, Montine TJ: Cerebral cortical Abeta42 and PHF-tau in 325 consecutive brain autopsies stratified by diagnosis, location, and APOE. J Neuropathol Exp Neurol 2015, 74:100–109
29. Postupna N, Rose SE, Bird TD, Gonzalez-Cuyar LF, Sonnen JA, Larson EB, Keene CD, Montine TJ: Novel antibody capture assay for paraffin-embedded tissue detects wide-ranging amyloid beta and paired helical filament-tau accumulation in cognitively normal older adults. Brain Pathol 2012, 22:472–484
30. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al: Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 2013, 45: 1452–1458
31. Escott-Price V, Bellenguez C, Wang LS, Choi SH, Harold D, Jones L, et al: Gene-wide analysis detects two new susceptibility genes for Alzheimer's disease. PLoS One 2014, 9:e94661
32. Jun G, Ibrahim-Verbaas CA, Vronskaya M, Lambert JC, Chung J, Naj AC, et al: A novel Alzheimer disease locus located near the gene encoding tau protein. Mol Psychiatry 2015, 2016, 21:108–117
33. Nalls MA, Plagnol V, Hernandez DG, Sharma M, Sheerin UM, Saad M, Simon-Sanchez J, Schulte C, Lesage S, Sveinbjornsdottir S, Stefansson K, Martinez M, Hardy J, Heutink P, Brice A, Gasser T, Singleton AB, Wood NW: Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet 2011, 377:641–649
34. Lill CM, Roehr JT, McQueen MB, Kavvoura FK, Bagade S, Schjeide BM, et al: Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: the PDGene database. PLoS Genet 2012, 8:e1002548
35. Beecham GW, Dickson DW, Scott WK, Martin ER, Schellenberg G, Nuytemans K, Larson EB, Buxbaum JD, Trojanowski JQ, Van Deerlin VM, Hurtig HI, Mash DC, Beach TG, Troncoso JC, Pletnikova O, Frosch MP, Ghetti B, Foroud TM, Honig LS, Marder K, Vonsattel JP, Goldman SM, Vinters HV, Ross OA, Wszolek ZK, Wang L, Dykxhoorn DM, Pericak-Vance MA, Montine TJ, Leverenz JB, Dawson TM, Vance JM: PARK10 is a major locus for sporadic neuropathologically confirmed Parkinson disease. Neurology 2015, 84:972–980
36. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Hurtig HI, Van Deerlin VM, Ritz B, Rausch R, Rhodes SL, Factor SA, Wood-Siverio C, Quinn JF, Chung KA, Peterson AL, Espay AJ, Revilla FJ, Devoto J, Hu SC, Cholerton BA, Wan JY, Montine TJ, Edwards KL, Zabetian CP: APOE, MAPT, and SNCA genes and cognitive performance in Parkinson disease. JAMA Neurol 2014, 71:1405–1412
37. Srivatsal S, Cholerton B, Leverenz JB, Wszolek ZK, Uitti RJ, Dickson DW, Weintraub D, Trojanowski JQ, Van Deerlin VM, Quinn JF, Chung KA, Peterson AL, Factor SA, Wood-Siverio C, Goldman JG, Stebbins GT, Bernard B, Ritz B, Rausch R, Espay AJ, Revilla FJ, Devoto J, Rosenthal LS, Dawson TM, Albert MS, Mata IF, Hu SC, Montine KS, Johnson C, Montine TJ, Edwards KL, Zhang J, Zabetian CP: Cognitive profile of LRRK2-related Parkinson's disease. Mov Disord 2015, 30:728–733
38. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, Van Deerlin VM, Ritz B, Rausch R, Factor SA, Wood-Siverio C, Quinn JF, Chung KA, Peterson-Hiller AL, Goldman JG, Stebbins GT, Bernard B, Espay AJ, Revilla FJ, Devoto J, Rosenthal LS, Dawson TM, Albert MS, Tsuang D, Huston H, Yearout D, Hu SC, Cholerton BA, Montine TJ, Edwards KL, Zabetian CP: GBA variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease. Mov Disord 2015, [Epub ahead of print]. doi:10.1002/mds.26359.

39. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergstrom M, Savitcheva I, Huang GF, Estrada S, Ausen B, Debnath ML, Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Langstrom B: Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 2004, 55:306–319
40. Villemagne VL, Fodero-Tavoletti MT, Masters CL, Rowe CC: Tau imaging: early progress and future directions. Lancet Neurol 2015, 14:114–124
41. Motter R, Vigo-Pelfrey C, Kholodenko D, Barbour R, Johnson-Wood K, Galasko D, Chang L, Miller B, Clark C, Green R, Olson D, Southwick P, Wolfert R, Munroe B, Lieberburg I, Seubert P, Schenk D: Reduction of beta-amyloid peptide42 in the cerebrospinal fluid of patients with Alzheimer's disease. Ann Neurol 1995, 38: 643–648
42. Galasko D, Clark C, Chang L, Miller B, Green RC, Motter R, Seubert P: Assessment of CSF levels of tau protein in mildly demented patients with Alzheimer's disease. Neurology 1997, 48: 632–635
43. Arai H, Morikawa Y, Higuchi M, Matsui T, Clark CM, Miura M, Machida N, Lee VM, Trojanowski JQ, Sasaki H: Cerebrospinal fluid tau levels in neurodegenerative diseases with distinct tau-related pathology. Biochem Biophys Res Commun 1997, 236:262–264
44. Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Cedarbaum J, Donohue MC, Green RC, Harvey D, Jack CR Jr, Jagust W, Morris JC, Petersen RC, Saykin AJ, Shaw L, Thompson PM, Toga AW, Trojanowski JQ: Impact of the Alzheimer's Disease Neuroimaging Initiative, 2004 to 2014. Alzheimers Dement 2015, 11:865–884
45. Skillback T, Farahmand BY, Rosen C, Mattsson N, Nagga K, Kilander L, Religa D, Wimo A, Winblad B, Schott JM, Blennow K, Eriksdotter M, Zetterberg H: Cerebrospinal fluid tau and amyloid-beta1-42 in patients with dementia. Brain 2015, 138(Pt 9): 2716–2731
46. Kang JH, Irwin DJ, Chen-Plotkin AS, Siderowf A, Caspell C, Coffey CS, Waligorska T, Taylor P, Pan S, Frasier M, Marek K, Kieburtz K, Jennings D, Simuni T, Tanner CM, Singleton A, Toga AW, Chowdhury S, Mollenhauer B, Trojanowski JQ, Shaw LM: Association of cerebrospinal fluid beta-amyloid 1-42, T-tau, P-tau181, and alpha-synuclein levels with clinical features of drug-naive patients with early Parkinson disease. JAMA Neurol 2013, 70:1277–1287
47. The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol 2011, 95:629–635
48. Niethammer M, Tang CC, Ma Y, Mattis PJ, Ko JH, Dhawan V, Eidelberg D: Parkinson's disease cognitive network correlates with caudate dopamine. Neuroimage 2013, 78:204–209
49. Brooks DJ: Imaging dopamine transporters in Parkinson's disease. Biomark Med 2010, 4:651–660
50. Backstrom DC, Eriksson Domellof M, Linder J, Olsson B, Ohrfelt A, Trupp M, Zetterberg H, Blennow K, Forsgren L: Cerebrospinal fluid patterns and the risk of future dementia in early, incident Parkinson disease. JAMA Neurol 2015, 72:1175–1182
51. Toledo JB, Korff A, Shaw LM, Trojanowski JQ, Zhang J: CSF alpha-synuclein improves diagnostic and prognostic performance of CSF tau and Abeta in Alzheimer's disease. Acta Neuropathol 2013, 126: 683–697
52. Sieber BA, Landis S, Koroshetz W, Bateman R, Siderowf A, Galpern WR, Dunlop J, Finkbeiner S, Sutherland M, Wang H, Lee VM, Orr HT, Gwinn K, Ludwig K, Taylor A, Torborg C, Montine TJ: Prioritized research recommendations from the National Institute of Neurological Disorders and Stroke Parkinson's Disease 2014 conference. Ann Neurol 2014, 76:469–472
53. Kang JH, Ryoo NY, Shin DW, Trojanowski JQ, Shaw LM: Role of cerebrospinal fluid biomarkers in clinical trials for Alzheimer's disease modifying therapies. Korean J Physiol Pharmacol 2014, 18: 447–456
54. Mills SM, Mallmann J, Santacruz AM, Fuqua A, Carril M, Aisen PS, et al: Preclinical trials in autosomal dominant AD: implementation of the DIAN-TU trial. Rev Neurol (Paris) 2013, 169:737–743
55. Reiman EM, Langbaum JB, Fleisher AS, Caselli RJ, Chen K, Ayutyanont N, Quiroz YT, Kosik KS, Lopera F, Tariot PN: Alzheimer's Prevention Initiative: a plan to accelerate the evaluation of presymptomatic treatments. J Alzheimers Dis 2011, 26 Suppl 3: 321–329
56. Sperling RA, Rentz DM, Johnson KA, Karlawish J, Donohue M, Salmon DP, Aisen P: The A4 study: stopping AD before symptoms begin? Sci Transl Med 2014, 6:228fs13

Senator BLUNT. Thank you, Dr. Grabowski. Dr. Schultz-Cherry.

STATEMENT OF STACEY SCHULTZ–CHERRY, PHD, MEMBER, DEPARTMENT OF INFECTIOUS DISEASES, ST. JUDE CHILDREN'S RESEARCH HOSPITAL, MEMPHIS, TENNESSEE

Dr. SCHULTZ-CHERRY. Yes. Chairman Blunt, Ranking Member Murray, and distinguished subcommittee members, thank you for inviting me to share my perspective on "Saving Lives Through Medical Research."

As you may know, St. Jude's mission is to advance cures and means of prevention for pediatric and catastrophic diseases through research and treatment. Since St. Jude opened its doors in 1962, no child is denied its treatment based on race, religion, or a family's ability to pay.

What you may not know is that St. Jude has also been on the forefront of the ongoing battle with pandemic influenza as well as other emerging viruses. In addition to my faculty position, I serve as the Deputy Director of the World Health Organization Collaborating Center for Influenza that is based at St. Jude. We focus solely on threats to humans from animal viruses and we work closely with WHO (World Health Organization) centers around the world to guide both research and response. We also produce and distribute materials for vaccines to use against emerging viruses.

Today, what I would really like to focus on is how critical it is to have adequate funding for infectious diseases really focused on four main points: threat, competition, preparation, and discovery. Zika, Ebola, antibiotic-resistant bacteria, influenza, even measles and mumps have highlighted how important infectious disease research is.

Since 1980, approximately one to three new human infections have been identified each year, either emerging or reemerging, many from animal sources. And while many of these were originally thought to be problems of the developing world, Ebola and Zika highlights that these viruses and these microbes have no boundaries.

The cost of these outbreaks is staggering, both in terms of economics and the impact on human health. Take for example Zika. It's really called the epidemic of delay. We know the impact of babies born to infected mothers or people developing Guillian-Barre syndrome, but what's actually going to happen 10 years from now from people that have been infected and perhaps didn't realize that they were? We really have no idea and this remains to be seen and researched.

Further, we have diseases in our own backyard considered neglected diseases of poverty that happen all throughout the Southern United States. This is not the developing world. This is in our own backyard and we need to better research this threat.

So how do we prepare for these continued threats? Stable funding from the NIH is key to building relationships with researchers within the U.S. as well as outside the U.S., especially in areas considered high risk. And we know from our work at St. Judge that this actually works.

So in the late 1990s St. Jude was awarded a contract from the National Institutes of Health to study influenza viruses across the world. We have built partnerships throughout many parts of the

world, including Southeast Asia. And while we were studying influenza virus, what actually happened is we—our partners ended up discovering, isolating, and identifying, the causative virus of SARS.

Because of the success of these contracts, we now have a network of Centers of Excellence for Influenza Research throughout the U.S. that is doing research, training people in infectious diseases, and they're now at the forefront of both influenza as well as emerging infectious diseases. The Center for Excellence researchers have actually also been involved in MERS and now Zika virus. It also allows us to provide critical information to the World Health Organization and the CDC to support global public health.

And really if you have questions whether these threats are real, in the past 3 days we've seen an outbreak of highly pathogenic avian influenza virus in poultry in Tennessee and now one in Wisconsin.

Competition. The U.S. has long been a leader in the biomedical research world. Unfortunately, we are seeing a disturbing trend in the number of patents being awarded to U.S. researchers as well as even submissions of publications to papers. One of the leading infectious disease journals found a disturbing trend that from 2010, 75 percent of—actually, 60 percent of submissions were from U.S. based scientists dropping to 37 percent in 2015. While there are many reasons for this, it is something that requires careful analysis.

Part of the preparation is training our next generation of scientists. And this is something I take very seriously, especially as my incoming role of the President of the American Society for Virology. There's a disturbing trend that many of our trainees do not want to pursue academic research. And one of the reasons is they're concerned about funding because they know funding equals success. In fact, one of my own trainees who is outstanding has taken a position in Cambodia because he's afraid of this.

And finally, it is discovery. Without basic research, we are not going to find the universal flu vaccine or new antibiotics, and so this is crucial for the future of the U.S.

[The statement follows:]

PREPARED STATEMENT OF DR. STACEY SCHULTZ-CHERRY

Chairman Blunt, Ranking Member Murray, and distinguished Subcommittee Members, thank you for inviting me to share my perspective on "Saving Lives through Medical Research." My name is Dr. Stacey Schultz-Cherry, and I am a member of the faculty in the Department of Infectious Diseases at St. Jude Children's Research Hospital in Memphis, Tennessee. As you may know, St. Jude's mission is to advance cures and means of prevention for pediatric catastrophic diseases through research and treatment. Since St. Jude opened its doors in 1962, no child is denied treatment based on race, religion or a family's ability to pay.

St. Jude also is at the forefront of the ongoing battle against pandemic influenza as well as other emerging viruses. In addition to my faculty position, I serve as the Deputy Director of the World Health Organization (WHO) Collaborating Center for Influenza at St. Jude, which is focused exclusively on the threat to humans from influenza viruses that emerge from animals. We work closely with other WHO centers around the world to guide global influenza research and response. St. Jude produces and distributes materials for vaccines for use against emerging viruses, including pandemic threats.

As an institution, St. Jude is grateful for the wonderful relationships we have with so many Members of this Subcommittee and your staffs, and we welcome all of you to visit us in Memphis to see what a difference our work makes in the lives of the children around the globe.

Today I would like to talk about how critical it is to have adequate funding for medical research and the consequences of insufficient support for basic research on infectious diseases. Federal support for medical research is critical to be prepared for the threat of emerging and reemerging diseases, to secure the United States' position as a global leader in medical research, to ensure that as a country we are able to attract and retain the brightest minds to medical research, and to continue to create the conditions under which ground-breaking medical discoveries are made. I will address each of these in turn.

Threat: Ongoing Threats Posed by Emerging and Reemerging Diseases

Zika, Ebola, antibiotic-resistant bacteria, Chagas, SARS and MERS, influenza viruses, even measles and mumps: these are just a few examples of the recent threats we have faced from emerging and re-emerging infectious diseases. Since 1980, approximately one to three new human infectious diseases have been identified each year; others have "re-emerged," causing greater numbers of cases than before and/or affecting different populations and regions than in the past.[1] According to the Centers for Disease Control and Prevention (CDC), greater than 60 percent of all known infectious diseases in people are spread from animals and 75 percent of the new or emerging infectious diseases in people have an animal source.

While many of these infections historically have been problems of the developing world, the recent Ebola and ongoing Zika outbreaks in the United States highlight that infectious diseases know no boundaries. During the Munich Security Conference in February 2017, Bill Gates was quoted as saying "Whether it occurs by a quirk of nature or at the hand of a terrorist, epidemiologists say a fast-moving airborne pathogen could kill more than 30 million people in less than a year. And they say there is a reasonable probability the world will experience such an outbreak in the next 10 to 15 years."

The cost of these outbreaks is staggering. Estimates of the economic cost of an influenza pandemic range from $374 billion (in 2014 US dollars) for a mild pandemic to $7.3 trillion for a severe pandemic with 12.6 percent loss of gross domestic product (GDP).[2] The cost to human life could be even greater. Take for example Zika virus, which has been called an "epidemic on delay." The impact on babies born to infected mothers or people developing Guillian-Barre syndrome after infection are well-appreciated, but the long-term effects of the epidemic are unknown. Whether infection results in future health effects or long term neurological deficits in infected people of all ages remains to be seen.

Further, there is a burden of disease caused by a group of infections typically only seen in the developing world that is largely hidden and that is known as the neglected infections of poverty. These diseases occur primarily in the Mississippi Delta and elsewhere in the Southern United States, as well as in disadvantaged urban areas and peoples living in Appalachia.[3] In several of these areas, many of the diseases we are most concerned about such as Zika, dengue, and diseases of animals that can transmit to humans (for example rabies), not only occur but thrive and could be a source for a widespread disease threat.

How do we prepare for these continued threats? Stable funding for the National Institutes of Health (NIH) to build relationships and capacity with partners across the United States, especially in these areas considered "high risk", and around the world is key not just to preparing for but possibly predicting the next emerging/re-emerging infectious disease threats. These monies must go beyond the basic research, and must include research and surveillance at the animal-human interface, which is the source of most emerging infectious diseases.

We know from our own work at St. Jude Children's Research Hospital that this approach works. The 1997 outbreak of highly pathogenic H5N1 avian influenza in humans in Hong Kong highlighted the need for global influenza surveillance to protect human health. In response, in 1999, the National Institute for Allergy and Infectious Diseases (NIAID) awarded a contract to St. Jude to set up continuous surveillance of aquatic birds and live bird markets in Hong Kong in collaboration with partners in Hong Kong, Southeast Asia, and the United States. In addition to this early warning system, this contract provided training and capacity building in this region of the world and fed invaluable information and reagents into the WHO and

---

[1] Jones, K. E. et al. Global trends in emerging infectious diseases. Nature 451, 990–993, doi:10.1038/nature06536 (2008).

[2] Pike, J., Bogich, T., Elwood, S., Finnoff, D. C. & Daszak, P. Economic optimization of a global strategy to address the pandemic threat. Proceedings of the National Academy of Sciences of the United States of America 111, 18519–18523, doi:10.1073/pnas.1412661112 (2014).

[3] Hotez, P. J. Reinventing Guantanamo: from detainee facility to Center for Research on Neglected Diseases of Poverty in the Americas. PLoS neglected tropical diseases 2, e201, doi:10.1371/journal.pntd.0000201 (2008).

CDC influenza response systems. Ultimately, this program developed a candidate seed vaccine strain. An unexpected second benefit of this program was the detection and characterization of the causative virus of SARS in 2003 by one of our Hong Kong collaborators, Dr. Malik Peiris.

Given the success of the initial contract awarded to St. Jude, NIAID established the Centers for Excellence in Influenza Research and Surveillance (CEIRS) network. The first 7 year contract, which funded five centers, resulted in the expansion of animal influenza surveillance programs internationally and domestically and focused on several high priority areas in influenza research. These projects provided key information on influenza virus-induced disease and immunity, assisted in the development of the Influenza Research Database, (an NIAID-funded program that provides datasets and bioinformatics tools to the global research community), and made important contributions to influenza reagent developments and data sharing. Equally important were the training and lab capacity-building activities the Centers supported within the U.S. and around the world. These activities enhance influenza research and response, and build infrastructure that can be applied to other infectious diseases. Arguably, some of the most important activities under the 2007–2014 contracts were a response to the 2009 H1N1 pandemic, in which the CEIRS network was instrumental in conducting early virus characterization studies and pre-clinical evaluation of vaccine material.

We are now in our second generation of the CEIRS network contracts. While the focus remains on influenza viruses, we have seen the emergence of MERS and Zika viruses. The response capabilities and collaborations established with partners within the U.S. and around the world have made it possible for the CEIRS network to rapidly respond to any emerging threat. CEIRS scientists again were among the first to identify and characterize the virus that causes MERS, determine that camels were a key source for human infections, and continue to "look for" MERS in animal and humans around the world. The new capabilities conferred through CEIRS also allowed us to respond to Zika rapidly. Given our long-term CEIRS-funded studies in Colombia, South America, NIH was able to establish Zika studies quickly in an area with an emerging Zika epidemic. However, our studies go beyond Zika infection. We want to understand what happens to a pregnant woman and her child when she gets co-infected with influenza virus and Zika, dengue or even chikungunya virus, a real threat to pregnant women throughout the Americas, especially in an influenza epidemic year like we are facing currently. These critical studies for human health would be impossible without sustained NIH funding.

If there were any doubt that these threats are real and can strike at any time, the USDA APHIS confirmed on Monday that highly pathogenic avian H7 influenza virus was identified in a commercial breeder flock in Lincoln County, Tennessee. The source of the virus appears to be wild birds. The threat to humans is currently unknown.

Competition: The U.S. as a Global Leader in Medical Research

The U.S. long had been the leader in biomedical research. Unfortunately, this trend is changing. A recent publication by Moses, et al. in the Journal of the American Medical Association (JAMA) used publicly available data from 1994 to 2012 to show that the decrease in US funding for biomedical research correlated with a decrease in the U.S. share of life sciences patents, with those considered most valuable decreasing from 73 percent in 1981 to 59 percent in 2011.[4]

This is also evident when reviewing publications from U.S. and foreign investigators. In 2009, the U.S. led the world in research productivity, with 33 percent of published biomedical research articles and numbers of articles from U.S. investigators increasing at 0.6 percent per year from 2000 to 2009. We also led the world in the numbers of most highly cited biomedical research articles with 63 percent of the top cited articles in 2000 and 56 percent in 2010. Yet, during the same period, the number of articles published in China increased by 18.7 percent annually and the number of highly cited literature from China continued to increase. After controlling for the share of the world's biomedical research articles using a citation index, publications from the U.S. declined −0.2 percent from 2000 to 2010 per year as the rest of the world increased by approximately 1 percent per year.[4] The trend is even more concerning when considering the number of biomedical research articles submitted to major infectious disease journals.

[4] Moses, H., 3rd et al. The anatomy of medical research: US and international comparisons. Jama 313, 174–189, doi:10.1001/jama.2014.15939 (2015).

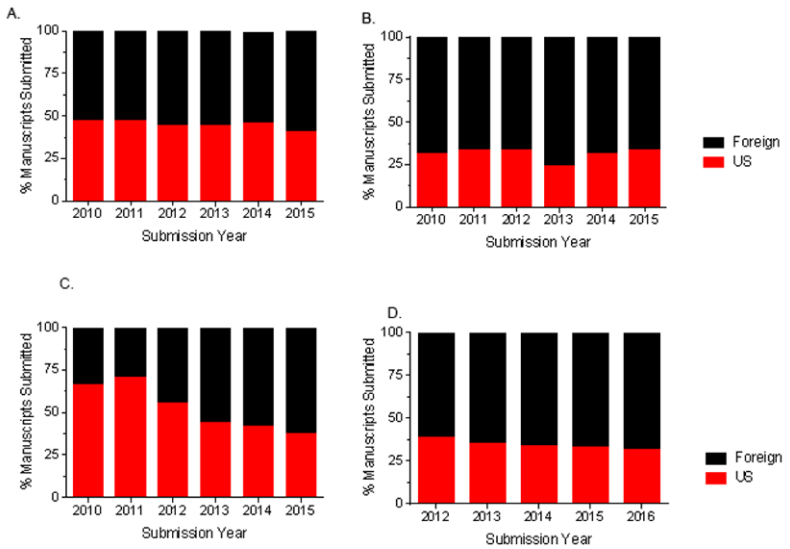

Figure 1. US and foreign submission trends for four major US-based infectious diseases journals.

Figure 1 illustrates the trends from four major infectious disease journals from 2010 through 2016. Overall, the number of submissions from foreign investigators has continued to increase as compared to those from U.S.-based scientists, but there are a few trends. In one journal, U.S.-based submissions were consistently lower than those received from foreign investigators (Figure 1B). However, most journals showed progressive decreases in submissions from US-based investigators. Figure 1C highlights a dramatic shift in one journal; where in 2010 60 percent of submissions were from U.S.-based scientists dropping to 37 percent in 2015. In all cases, the majority of foreign-based submissions come from China.

There are different explanations for these changes, and understanding journal trends and US competitiveness in scientific research will require careful analysis.

Preparation: Encouraging the Next Generation of Medical Researchers

A key to fighting infectious disease threats is training the next generation of scientists, including the physician-scientists and Doctor of Veterinary Medicine-scientists that likely will be at the frontline of the fight. One of the highlights of my career has been mentoring the next generation of scientists. It is something that I take seriously and will be a major focus during my term as the President of the American Society for Virology. Yet over the past 5 years, we have seen a disturbing trend: increased numbers of trainees do not want to pursue faculty positions in an academic setting. A recent study by the University of California at San Francisco (UCSF), a world renowned biomedical research institution, tracking their trainees' careers showed that only 37 percent of U.S.-employed postdoctoral alumni were in faculty positions, which included non-tenure track faculty-like full time research or teaching positions with the majority of these employed at research institutions. The outcome is very different for UCSF postdoctoral alumni that left the U.S. In that case, 54percent were in faculty positions.[5]

When I ask a trainee why he or she does not want to pursue a career in academic research, not receiving NIH funding is a primary concern. Trainees know that the lack of funding will make it difficult to be productive and ultimately obtain tenure. The low NIH payline (determined by the score you receive during the peer review

[5] Silva, E. A., Des Jarlais, C., Lindstaedt, B., Rotman, E. & Watkins, E. S. Tracking Career Outcomes for Postdoctoral Scholars: A Call to Action. PLoS biology 14, e1002458, doi:10.1371/journal.pbio.1002458 (2016).

process) also requires that young investigators spend more time writing grants rather that performing research.[6,7] Stability of funding may be even more important for the careers of young scientists than the overall size of the Department of Health and Human Services or NIH. Boom-and-bust cycles wipe out generations of young scientists and discourage people from taking a chance in research careers. This means that only older scientists stay in the game. In 2011, the average age of first-time R01 grantees was 42 for Ph.D.s and mid-to-late 40s for M.D. and M.D.-Ph.D. scientists. It is likely even higher now. We also are seeing a skewing in the age of NIH-funded Principal Investigators (PIs). In the 1980s the majority were 35 and younger with less than 1 percent over age 66. Since the 2000's this has reversed, with the majority of NIH PIs now older than 66.

In many cases, young investigators are required to have funding before they even can apply for faculty positions, making it difficult if not impossible for many to find their first "real job." "Erik" is an example of this. He came to my laboratory as a postdoctoral fellow to study the impact of obesity on influenza infection and vaccination response, after receiving his Ph.D. in nutrition from the University of North Carolina at Chapel Hill. This is a very creative, ambitious and productive young scientist at the interface of nutrition and infectious diseases. In spite of an outstanding CV, he was having difficulties finding a faculty position because he did not already have independent NIH funding. Many departments were concerned that it could be difficult for him to obtain funding for his work, despite the cutting edge research he was doing. Instead of staying in the U.S., Erik has decided to accept a position as the Head of Virology at one of the Institute-Pasteur laboratories. While I am excited to see him begin his independent career and know that he will be successful, it is discouraging that he has to leave the U.S. to pursue his dreams to be a PI.

It is not only the careers of young investigators that are of concern, but those of the mid-level PIs like me. In many cases, we are the "workhorses" of our fields, serving as journal editors, NIH study section members, teachers for undergraduate, graduate, medical, and professional students, heads of admissions committees, even becoming Presidents of our respective societies. Yet unlike our more junior colleagues, we are "too old" to apply for many of the funding opportunities specific for young investigators, and may not have the "name recognition" of our more senior colleagues. While on the faculty at the University of Wisconsin-Madison, several of my colleagues at the Associate Professor-level and even Professor-level had to close their research laboratories due to a lack of funding. While they were able to provide other invaluable contributions to the department and university it was a significant loss to basic research. In summary, not only are we failing to bring young people into infectious disease research, but we also are losing many of our "soldiers" in the fight. This will leave us ill-prepared to face future threats, which we know will continue.

Discovery: Basic Research is the Foundation for Important Medical Discoveries

Federal funding for basic research is an important foundation of societal progress, sustainability, economy and obviously the health and well-being of the population.[8] Without funding for basic research and especially funding for high-risk, innovative research, we will never develop a universal influenza vaccine, new antibiotics to combat antibiotic resistant microbes, or crucial new cancer therapies. In terms of infectious disease research, in order to be at the forefront of the next threat, we need to understand what is happening in our animal populations (domestic and wildlife), and appreciate that our population is aging and expanding, which can impact infectious disease emergence, transmission, disease severity and even efficacy of our therapeutic strategies.

Over the weekend, a global electronic reporting system for outbreaks of emerging infectious diseases and toxins called "ProMED-mail" posted notifications on new meningococcal meningitis, measles and mumps outbreaks on college campuses across the US; the continued westward spread of highly pathogenic avian H5 influenza virus; four new human cases of avian H7N9 influenza infection in humans; and an outbreak of an undiagnosed respiratory disease in Hong Kong, all highlighting the ongoing threat posed by infectious diseases. The next Jonas Salk, George Washington Carver, Marie Curie, or Jane Goodall may be working in our laboratories. Let's not lose any of them.

---

[6] Daniels, R. J. A generation at risk: young investigators and the future of the biomedical workforce. Proceedings of the National Academy of Sciences of the United States of America 112, 313–318, doi:10.1073/pnas.1418761112 (2015).

[7] Powell, K. Young, talented and fed-up: scientists tell their stories. Nature 538, 446–449, doi:10.1038/538446a (2016).

[8] Murray, D. L. et al. Bias in Research Grant Evaluation Has Dire Consequences for Small Universities. PloS one 11, e0155876, doi:10.1371/journal.pone.0155876 (2016).

* * * *

I extend my sincere appreciation to the Subcommittee for asking me to share my views with you today, and I look forward to answering any questions you have.

Senator BLUNT. Thank you, Dr. Schultz-Cherry. Dr. Sasser.

STATEMENT OF JENNIFER SASSER, PHD, ASSISTANT PROFESSOR, UNIVERSITY OF MISSISSIPPI MEDICAL CENTER, JACKSON, MISSISSIPPI

Dr. SASSER. Chairman Cochran, Chairman Blunt, Vice Chairman Leahy, and Ranking Member Murray, and members of the subcommittee, thank you for the opportunity to appear before the subcommittee today. I am Jennifer Sasser, an Assistant Professor in the Departments of Pharmacology and Physiology at the University of Mississippi Medical Center.

I would like to thank the committee for its steadfast support of the National Institutes of Health and for medical research in general. The funding provided by Congress ensures that the body of knowledge for both discovery and translational research applications continues to grow to the benefit of all Americans. This steady support is critical to my future, the future of my students and research assistants, and most importantly, to the countless people who will receive better care due to the work funded by NIH.

My research mission is to better understand and treat preeclampsia, a disease of high blood pressure during pregnancy. Preeclampsia endangers mothers during pregnancy and increases their risk of later heart attacks, strokes, and kidney disease. In addition, this disease puts the lives and futures of newborns at risk from the very start with the resulting births costing Mississippi $330 million a year. Identifying better treatments for preeclampsia and reducing pre-term birth will have a direct impact on the health of mothers and children in Mississippi and nationwide while reducing the cost to treat them.

Being an early career researcher today comes with a unique set of challenges. The pressure to win grants is palpable and the competition for funding is stronger than ever. This competitive environment leads to few awards, most of which are won by seasoned veterans at select institutions making it hard for young investigators to get a toehold in the research world.

The Institutional Development Award, or IDeA program, has provided critical support to Mississippi researchers for years funding a number of groundbreaking projects across the State. This program allows us to compete on a more level playing field increasing our ability to secure funding. Thanks to IDeA support, my research program is now competing successfully with top programs in the country.

At the end of last year, an editorial in ASBMB Today entitled "Send My Tax Dollars to Mississippi" stated that taxpayers net more scientific publications by funding investigators at the University of Mississippi Medical Center than by giving the funds to prestigious and top ranked institutions. This article underscores what I have learned firsthand, that the IDeA program is a good investment, benefitting taxpayers, the research community, and the recipient States.

The pressure to secure grants compounded by low funding rates can often by a career ender for talented and highly trained young investigators. As the Director of our graduate program in Medical Pharmacology, this is a dilemma that I and others face every year when we decide which students we can accept into our PhD program. How can we responsibly train students for careers that may not be sustainable in the future? How many students should we take when the number of positions after graduation is decreasing?

Of course, we emphasize the many career paths available to biomedical PhD graduates, but we have to balance our enthusiasm for training the next generation of biomedical researchers with the harsh realities of highly competitive funding, fewer academic positions, and reductions in workforce in pharmaceutical and biotechnology industries.

I am fortunate to have benefitted not only from Mississippi's IDeA State status, but also from vital assistance from the NHLBI (National Heart, Lung, and Blood Institute) and the NIDDK (National Institute of Diabetes and Digestive and Kidney). As a postdoctoral fellow, my stipend was supported by an Institutional Training Grant from the NHLBI, which allowed me the time to develop the skills necessary for this career path. I then successfully competed for a career development award from the NIDDK which allowed me to fully establish myself as an independent scientist. These training and career development programs are essential for continuing our pipeline of scientists in the coming generations. And I credit these programs for kick-starting my career and giving me the stability and confidence to pursue a lifetime in biomedical research.

In January, I received the notice of award for my first R01 grant, the gold standard grant mechanism. I would not have reached this goal so quickly without the commitment of the NHLBI to early stage investigators. This additional support is critical to young researchers who face tenure deadlines and may be denied the opportunity to continue their careers if they do not meet this R01 milestone. Without NIH support, many labs are forced to downsize or completely shut down, forfeiting years of investment in that researcher's training, as well as training positions for fellows, students, and employment opportunities.

With this R01 award, I will grow my laboratory to support additional PhD students and research assistants, increasing the number of trainees as well as high quality jobs in the State.

On behalf of many young researchers, I urge you to continue to provide funds for early career programs like these and encourage NIH to explore how other agencies might enhance their programs to support fledgling investigators.

Thank you for the opportunity to appear before the committee and I am happy to answer any questions.

[The statement follows:]

PREPARED STATEMENT OF JENNIFER M. SASSER, PH.D.

Chairman Cochran, Chairman Blunt, Vice Chairman Leahy and Ranking Member Murray, thank you for the opportunity to appear before the Subcommittee today. I am Jennifer Sasser, an Assistant Professor in the Departments of Pharmacology and Physiology at the University of Mississippi Medical Center.

I would like to thank the Committee for its steadfast support for the National Institutes of Health and for medical research in general. The funding provided by Congress ensures that the body of knowledge for both discovery and translational clinical applications continues to grow to the benefit of all Americans. This steady support is critical to my future, the future of my students and research assistants and, most importantly, to countless people who will receive better care due to the work funded by NIH.

My research mission is to better understand and treat preeclampsia, a disease of high blood pressure during pregnancy. Preeclampsia endangers mothers during pregnancy and increases their later risk of heart attacks, stroke and kidney disease. In addition, this disease (I omitted the word ALSO here) puts the lives and futures of newborns at risk from the very start, with the resulting preterm births costing Mississippi $330 million a year. Identifying better treatments for preeclampsia and reducing pre-term birth will have a direct impact on the health of mothers and babies in Mississippi and nationwide, while reducing the cost to treat them.

Being an early career researcher today comes with a unique set of challenges. The pressure to win grants is palpable, and the competition for funding is stronger than ever. This competitive environment leads to few awards, most of which are won by seasoned veterans at select institutions, making it hard for young investigators to get a toehold in the research world. The Institutional Development Award, or IDeA, program has provided critical support to Mississippi researchers for years, funding a number of groundbreaking projects across the State. This program allows us to compete on a more level playing field, increasing our ability to secure funding. Thanks to IDeA support, my research program is competing successfully with top programs in the country.

At the end of last year, an editorial in ASBMB Today entitled "Send My Tax Dollars to Mississippi" stated that "taxpayers net more scientific publications by funding investigators at the University of Mississippi Medical Center ... than by giving the funds to prestigious and top-ranked institutions." This article underscores what I've learned firsthand—that the IDeA program is a good investment, benefiting the taxpayers, the research community and the recipient States.

The pressure to secure grants, compounded by low funding rates, can often be a career ender for talented and highly trained young researchers. As the Director of our graduate program in Medical Pharmacology, this is a dilemma I and others face every year when deciding which students we can accept into our PhD program. How can we responsibly train students for careers that may not be sustainable in the future? How many should we take when the number of positions available after graduation is decreasing? Of course, we emphasize the many career paths available to biomedical PhD graduates, but we have to balance our enthusiasm for training the next generation of scientists with the harsh realities of highly competitive funding, fewer academic positions, and reductions in workforce in the pharmaceutical and biotechnology industries.

I am fortunate to have benefitted not only from Mississippi's IDeA state status, but also from vital assistance from the NHLBI and the NIDDK. As a postdoctoral fellow, my stipend was supported by an Institutional Training Grant from the NHLBI, which allowed me time to develop the skills needed for this career path. I then successfully competed for a career development award from the NIDDK which allowed me to fully establish myself as an independent scientist. These training and career development programs are essential for continuing our pipeline of scientists in the coming generations, and I credit these programs for kick-starting my career and giving me the stability and confidence to pursue a lifetime of work in medical research.

In January, I received a notice of award for my first R01 grant, the "gold standard" grant mechanism. I would not have reached this goal so quickly without the commitment of the NHLBI to Early Stage Investigators. This additional support is critical to young researchers who face tenure deadlines and may be denied the opportunity to continue their careers if they do not meet the R01 milestone. Without NIH support, many labs are forced to downsize or shut down, forfeiting years of investment as well as training positions for fellows and students and employment opportunities. With this R01 award, I will grow my laboratory to support additional PhD students and research assistants, increasing the number of trainees and high-quality jobs in the State. On behalf of the thousands of young researchers just getting their start, I urge you to continue to provide funds for early career programs like these and to encourage NIH to explore how other agencies might enhance their programs to support fledgling investigators.

I thank you for the opportunity to appear before the Committee today and am happy to answer any questions you may have.

Senator BLUNT. Thank you, Dr. Sasser.

Of course, we are pleased to have the Ranking Member of the Committee with us as well, not to mention the president pro tem emeritus of the Senate. So, Senator Leahy, if you'd like to make a comment this would be a good time.

STATEMENT OF SENATOR PATRICK J. LEAHY

Senator LEAHY. Thank you, Mr. Chairman.

I do thank you and Senator Murray for having this hearing. I think the medical research is one of the most vital things in our country. We have imminent scholars and speaking here and I would also mention in the University of Vermont medical researching funding opportunities are critical, and not only because of the research we do there, but the people it attracts there.

This commitment of what we've done this subcommittee has resolved billions of dollars of increase for NIH or the past year fiscal years, including the billions promised or the Twenty-First Center Cures Fill.

But I worry when we say, "Well, we've got to take money for things." $25 billion for a wall or the Mexican border which will have to come from somewhere in here, a huge increase in defense spending. I would urge all Senators, you can't hit a pause button on research. And, Dr. Grabowski, you talked about Alzheimer's. You can't say, "Oh, well, just stop the research for a few years and come back to it." Just, you can't in cancer or any other areas.

And so I think in the Appropriations Committee we can talk about our national priorities frankly. I think the big national priority is medical research. There is no family that doesn't know somebody or have a member of the family who has suffered from cancer or heart conditions, diabetes, even Alzheimer's. I can't imagine any American who thinks that we should cut back on research in they might say in the most powerful wealthiest nation on earth, why aren't we doing more?

So I'll put my whole statement in the record, Mr. Chairman, and I thank you.

[The statement follows:]

PREPARED STATEMENT OF SENATOR PATRICK J. LEAHY

I want to thank Chairman Blunt and Ranking Member Murray for holding this important hearing to discuss the importance of medical research in saving lives.

Medical research holds tremendous promise and is responsible for breakthroughs with diseases like cancer and Alzheimer's. Federal research dollars provide the Nation's top professions with the resources they need to continue expanding medical knowledge. The tireless devotion of researchers to finding cures has served as a catalyst for nationwide medical advancement.

At the University of Vermont, medical research funding opportunities are critical, not just for creating new medical advancements but for attracting the best faculty members and researchers to Vermont. Last year, research funding through NIH accounted for nearly $40 million at UVM, supporting hundreds of jobs and students. Research through the University has led to advancements in lung disease treatment, cancers, and more effectively using genome testing to advance precision medicine. I was proud to host Vice President Biden at the University of Vermont to discuss his Cancer Moonshot initiative and how Vermont is contributing to research to better treat—and hopefully cure—the disease.

This subcommittee has recognized the importance of funding medical research. This commitment has resulted in billions of dollars in increases for NIH over the last few fiscal years in addition to the billions of dollars promised with the passage of the 21st Century Cures bill in December.

Unfortunately, the progress we have made is in jeopardy as medical research funding and so many other programs are in the crosshairs for fiscal year 2018. Medical research cannot be turned on and off. Scientists don't hit "pause" on studies and continue the research when Federal funding resumes. The ups and downs of the budget are particularly harmful in the medical research field. Budding scientists and researchers might decide to seek other career paths, leaving fewer scientists and therefore, fewer scientific discoveries. We must prove to the world that we will stand firm on our commitment to medical research for generations to come.

President Trump has proposed a different approach. He wants to make deep cuts to domestic programs to pay for increased defense spending and to build a misguided and expensive wall on our southern border. President Trump seeks to implement this unbalanced agenda at the expense of other priorities that will affect all of us, especially when it comes to medical research. This is not only misguided policy, it flies in the face of the Budget Agreement which is meant to ensure parity between defense and non-defense spending.

The Appropriations Committee is where our national priorities are translated into reality. I look forward to working with this subcommittee and others to ensure that cuts are not made that would undermine our progress on medical research. I look forward to hearing from our witnesses today on the importance of medical research and how Federal contributions are critical.

Thank you, Chairman Blunt, for holding today's hearing.

Senator BLUNT. Thank you, Senator. We'll have a five-minute round of questions. And Senator Murray—I'll start and then recognize you.

PRECISION MEDICINE

Dr. Eberlein, you mentioned in treating breast cancer that the normal treatment would usually include surgery, then radiation, then chemotherapy. And you also said that your estimates would be that four out of five patients wouldn't need both radiation and chemotherapy. How do you determine that? What are you doing to try to help determine which four patients don't have to, one, pay for it, but more importantly go through the personal effort of having a treatment that they don't need? How do we know which ones would need it or how do you hope we figure out which patients need it and which patients don't?

Dr. EBERLEIN. So we are using molecular markers and genomic analysis of tumors. We've now identified approximately 98.6 percent of mutations associated with human malignancy, so we know what those are. And now the question is can we develop a relational database combining genomic information with clinical information to be able to recommend to an individual patient what her treatment should or should not be.

The greatest opportunity is probably in areas like early breast cancer, premenopausal breast cancer that I cited, where we may be able to solve this dilemma and identify the 80 percent who don't require further toxic therapies from the 20 percent who do. And we are now applying that kind of information in clinical trials through genomics and molecular markers from individual tumors of a particular patient.

The same is true, by the way, in colorectal cancer, stage II colorectal where 25 percent of those patients after surgery will have a recurrence. So these are dilemmas that we face across many of the tumor types of cancer, but the solution is going to be a similar type of solution.

Senator BLUNT. And 98.6 percent of mutations being determined—that you can determine enough or do you need to have understood 100 percent of mutations or what's the range here where

you would recommend to a patient in that foreseeable future that you really may not need this, but it is possible, so you should have chemo or we think there's almost no likelihood that chemo is necessary in this case?

Dr. EBERLEIN. Having 98 percent, sir, is a wonderful start. Obviously we are looking for the remaining 1.4 percent of driver mutations. That said, clearly we have developed relational databases based on the 98.6 percent that we do know and are applying those in breast cancer and lung cancer and other leukemias and other types of cancer.

ALZHEIMER'S DISEASE

Senator BLUNT. Thank you. Dr. Grabowski, in your work and your testimony, you mentioned that if we could delay onset of Alzheimer's by an average of 5 years that would reduce the future patient cost, the future patient population, or both. Would you talk about that a little bit?

Dr. GRABOWSKI. The incidents of Alzheimer's disease dementia doubles every 5 years after age 65. So if you could delay onset by 5 years you would cut the number of cases in half and by inference you could cut costs in half that are related to Alzheimer's dementia.

Senator BLUNT. Have you looked at the NIH projections on taxpayer cost of Alzheimer's?

Dr. GRABOWSKI. Yes.

Senator BLUNT. And what are those by say 2050? I think that was the outside number.

Dr. GRABOWSKI. So the number of cases that we have on our hands by 2050 will probably about triple. So we are talking trillions of dollars of direct and opportunity costs related to Alzheimer's dementia.

Senator BLUNT. I think there's a $1.1 trillion number out there of today's dollars which would be twice the Defense budget would be the taxpayer——

Dr. GRABOWSKI. Yes.

Senator BLUNT [continuing]. Money that would be spent on Alzheimer's. And, you know, we deal with these big numbers like $1.1 trillion and how much more is that than $1.1 billion? Hard to get a real sense of that until you think this is twice the Defense budget. If your work and other's work doesn't get us to a better place, not to mention the individual and family impact of what we see here the government will be the recipient of a very large bill.

Dr. GRABOWSKI. Yes. I think that is accurate.

Senator BLUNT. Senator Murray.

EFFECT OF PRECISION MEDICINE ON ALZHEIMER'S DISEASE

Senator MURRAY. Well, thank you very much, Dr. Grabowski. It's great to have you out here from the University of Washington.

Dr. GRABOWSKI. Thank you.

Senator MURRAY. Thanks for coming all the way across the country for this. University of Washington is home to one of the 15 Alzheimer's Disease Research Centers support with NIH funding and we really appreciate the great work you do.

I understand that a particular focus of the Center is to identify the key differences in the way the disease progresses to make it feasible to develop targeted treatments for people with different variants of Alzheimer's. The model here is cancer treatment, where we have seen notable advances in treatment of colon cancer, for example. Can you talk to us a little bit about why you are hopeful that a precision medicine approach could speed the development of effective treatments for Alzheimer's?

Dr. GRABOWSKI. Sure. Up to this point, Alzheimer's disease has been treated pretty much as one thing. All of the epidemiological studies that you've heard about have classified people as having Alzheimer dementia or not.

To a clinician who sees patients every week, it is amazing how many different ways people present with Alzheimer's disease. This is a disease with a lot of heterogeneity. Some people present too early. Some present much later. It doesn't affect all regions in the brain the same way and the pattern of brain regions that are involved differs across patients.

There are factors that we don't understand that affect the particular pattern of involvement and the severity of involvement. There are other pathways that we need to understand besides amyloid as a driver of disease.

When you look at recent genome wide association studies of later sporadic onset Alzheimer's disease, the genes that are being fingered are not amyloid production or processing genes, but things that have to do with innate immune responses, for example, or protein trafficking. So there are other pathways which are important and we need to understand which pathway is driving disease in which patient.

I mentioned in my opening remarks that there are trials going on which are treating pre-symptomatic people that have genetic abnormalities that destine them for Alzheimer disease driven by amyloid. So those treatment trials are very important and they can really be considered at precision medicine trial, but we need other pathways to be understood and to factor into our work.

AMYLOID TREATMENT

Senator MURRAY. The amyloid treatment that you mentioned, how early can you see that in someone that will develop Alzheimer's later?

Dr. GRABOWSKI. So we now have biomarkers that we can either develop from the spinal fluid or more compellingly, from imagining. So amyloid molecules can be detected in the brain 15 years in advance of symptoms. And so whereas at age 65 less than 1 percent of people have Alzheimer's dementia, fully 20 percent of people age 65 will have a positive amyloid scan. So that gives you an idea of the magnitude.

Senator MURRAY. Wow.

Dr. GRABOWSKI. So we hear about the coming tsunami of Alzheimer's disease. It's a tsunami with a big iceberg in it, you know, of latent disease. And you can look at that as an opportunity because that is a period of time when you could intervene before symptoms have caught up with people.

BARRIERS TO EFFECTIVE ALZHEIMER'S DISEASE TREATMENT

Senator MURRAY. Wow. Well, what are the greatest barriers to finding an effective treatment for this, for the disease?

Dr. GRABOWSKI. There are several barriers. One barrier is we just fundamentally understand why amyloid leads to toxicity in the brain. There's a lot of assumptions that are made there. It must be important, you know, just that an extra amyloid gene is enough to cause a family to have Alzheimer's disease, but there are factors that we don't understand. There are factors that have to do with why some people are resilient to the disease. There are people that have a genetic abnormality, but nevertheless don't develop Alzheimer's disease until much later. We don't understand that.

Education and cognitive lifestyle protect people for years. We don't understand what the brain mechanism of that is. We have relied on mouse models that haven't yet given us an effective treatment. We need human disease models. Some of the pluripotent stem cell models, as I mentioned in my opening remarks, are very promising for this.

Senator MURRAY. That sounds like funds, money, is the key, right?

Dr. GRABOWSKI. Yes. Yes. Yes. And then that is what—that is actually the point of the professional judgment budget.

PREVENTION OF HYPERTENSION AND CARDIOVASCULAR DISEASE

Senator MURRAY. Yes. Yes. And, Dr. Sasser, really quickly, CDC relies on resources from the prevention fund to make grants to programs in States and communities and through national organizations that are focused on prevention, early detection, and treatment of high blood pressure. As you know given your research into kidney disease, hypertension not only leads to that disease, but is a leading risk factor for heart disease, which is the Nation's number one cause of death. Can you tell us the efforts to education patients and providers and what they can do to prevent the development of hypertension or obesity or cardiovascular disease is needed?

Dr. SASSER. Yes, they are definitely needed. We have seen a huge increase in the number of obese people in our country. Children are developing obesity at very young ages and then this leads to more hypertension and cardiovascular disease. So these are very important focuses that we need to look at.

Recent numbers from the American Heart Association show that while we now spend about $338 million a year on cardiovascular disease and all the consequences of that as well as lost work time, et cetera, those costs are expected to rise to $1 trillion by 2030 if prevention programs are not effective in stopping this epidemic.

Senator MURRAY. Okay. Well, I would just say that the prevention fund money that is in the ACA is really critical. It's one of the reasons why I am very concerned about the repeal efforts. So thank you very much. I appreciate it.

Senator BLUNT. Thank you, Senator Murray. Senator Cochran.

CURES FOR CANCER

Senator COCHRAN. Mr. Chairman, I am glad to welcome Dr. Jennifer Sasser from the University of Mississippi Medical Center in

Jackson who is conducting research or involved in conducting research. I am advised that this is a research program that has national implications. I wonder how you can say about the extent to which we are making progress in finding a cure for cancers, whether your medical center has had national impact as we understood from our last hearing. I suppose a status report on how is it going. Are we making progress?

Dr. SCHULTZ-CHERRY. We are definitely making progress. With the advancement in precision medicine as well as the Pediatric Cancer Genome Project, we've been able to understand the underlying in many cases mechanisms for some of the childhood cancers that we see at St. Jude and then to target specific therapies to those particular cancers. And we are sharing this information with pediatric oncologists around the world and including our techniques so that they can use those in their own patients as well.

Senator BLUNT. Senator Durbin.

NIH FUNDING

Senator DURBIN. Thanks for this hearing. Thanks to Senator Murray who just stepped out and Senator Alexander. Senator Blunt, thanks to you. You've really made history with funding for the NIH and I am proud to be a small part of it and to encourage you every step of the way. It is the most bipartisan thing going on in Capitol Hill and I think we are all happy to hear that. There shouldn't be any partisanship at all involved in what we are setting out to do here and so we've tried to keep it that way.

We came to our efforts with the cures act, we said this is going to be supplemental. This is going to be additive. It isn't going to be in place of the NIH [inaudible]. And I hope we stick with that through the remainder of this year and then to the next year in budgeting as well. So, Senator Alexander, I know your personal commitment to it. You've talked to me about it many times. You're going to leave a great record if we do what we promised to do on this. Thank you for your leadership, again, with Senator Murray, who is a recurring theme in this whole conversation about medical research on the Democratic side.

DEPARTMENT OF ENERGY COLLABORATION

Dr. Grabowski, I met with the Secretary of Energy a couple of years ago and talked about Alzheimer's and I talked about the NIH budget. And he said, "Senator, do you have any idea where we are doing the research on imaging this disease?" I said, "Where would that be, Mr. Secretary?" He said, "The Office of Science and the Department of Energy." So can you tell me what collaboration is involved that you know of with Alzheimer's research and the Department of Energy?

Dr. GRABOWSKI. Well, that is a good question. I don't know a lot about that. The National Laboratories have been important. We work in our brain imaging research group at University of Washington with the Pacific Northwest National Lab and there are a number of other labs that have been pivotal over the years in developing PET (Positron Emission Tomography) imagining technology, in particular. PET imaging is becoming a mainstay of Alzheimer's disease research. We now have molecular tracers that de-

tect, as I mentioned earlier, the amyloid protein, and even more exciting, the tau protein, which is the component of neurofibrillary tangles that really marks the impact of this disease. We are very excited about the use of tau imaging as a treatment biomarker in the future.

ALZHEIMER'S DISEASE DETECTION

Senator DURBIN. So, forgive me. I am a liberal arts lawyer and you can lose me in a second when you get into this conversation.

Dr. GRABOWSKI. Yes. Yes.

Senator DURBIN. But is it possible for you to determine through some imaging of my tiny brain whether or not there is any evidence of Alzheimer's in my future?

Dr. GRABOWSKI. Yes. Yes, sir. So the amyloid protein deposits in the brain years in advance of the symptoms. If someone has memory impairment and they have a negative amyloid scan, it is not due to Alzheimer's disease. The reason that we don't use this clinically is it is hard to know what to do with someone who's got a normal cognition and a positive amyloid scan. We think on average people are destined to develop progressive difficulty. That's an area of active research. But in general we can tell a decade or more in advance that someone has the Alzheimer process going on in the brain.

ALZHEIMER'S DISEASE INTERVENTION

Senator DURBIN. A year or two ago I read that two major pharmaceutical companies were trying to develop something to slow down, intervene. Did I subsequently read that it didn't work or what is the status?

Dr. GRABOWSKI. Right. So there have been a number of negative trials, particularly of agents which have been designed to glom onto and remove amyloid protein from the brain. In general, those studies have been given—those treatments have been given to symptomatic individuals with mild Alzheimer dementia.

We wonder whether the failure of those trials has to do with the fact that it is given a little too late or maybe much too late. The trials which are going on now which I think are pivotal are the trials that are given in pre-symptomatic individuals that we know have amyloid driven disease who have mutations in the small number of genes that destine people for Alzheimer disease. There's two big trials going on, the DIAN Trials Unit, and the Alzheimer's Prevention Initiative, which is in a number of families and a big family that lives in Columbia, South America. And something called the A4 Trial, which is for people like us who have normal cognition but may have a positive amyloid scan at age 65 or older. Those studies are ongoing and I think, are the acid test for the amyloid treatment.

Senator DURBIN. Mr. Chairman, let me close with two brief remarks. First, Dr. Eberlein, Siteman is just recognized as one of the best and Barnes-Jewish in St. Louis and from my old home area really is a leader in research and treatment. Thank you for joining us as well as our other witnesses.

Dr. EBERLEIN. Thank you very much.

Senator DURBIN. And let me just also say we are going to know in a few days what we are facing in this budget. I am worried. I am on the Defense Appropriations Subcommittee. There's talk about putting a dramatic increase in Defense spending. We all want a strong national defense, but if it comes at the expense of some fundamentals like medical research then we are not really serving the people that we represent as we should. I hope that this next President's budget is sensitive to those realities. Thank you.

Senator BLUNT. Thank you, Senator Durbin. Thank you for your leadership on this research issue, particularly, and also to Senator Alexander, who's been one of the real advocates along with Senator Moran who was the chairman of this subcommittee before me. I think anybody on this panel sees a real commitment to continuing our commitment to research and the impact it has on lives, as well as the impact it has on taxpayers, as well as the impact it has on our capacity as a country.

So, Senator Alexander.

Senator ALEXANDER. Thanks, Mr. Chairman. Welcome to the witnesses. This Congress has been a little slow in finding things on which we can agree, but one thing we do agree on, as has been said, is the importance of biomedical research. And many of those who have led that fight are here and will continue to do it, I think especially of the work that Senator Blunt and Senator Murray did with the subcommittee. My hope is that we can approve the appropriation soon for the current year, which would give us two straight years in the subcommittee of increased NIH funding. And then the work that Senator Murray did with me and others on the 21st Century CURES Bill, we have a commitment there for future funding. Of course, Senator Durbin and Senator Cochran and Senator Moran have been at the forefront of that all along.

So we will continue to do that. I think it is important for those working in the community to notice that when we talk about a $2 billion increase in 1 year for the NIH that could be $20 billion over 10 years. When we talk about another $2 billion in the second year, that could be 20 more billion over 10 years. And when we talk about $4.8 billion in the 21st Century CURES Bill, that is on top of that. So these are beginning to be significant dollars.

UNIVERSAL FLU VACCINE

I want to ask Dr. Schultz-Cherry from St. Jude's—such a magnificent place—Dr. Francis Collins gave a little riff here last year about all the things, the miracles we might expect over the next 10 years and he talked about a vaccine for HIV/AIDS and a vaccine for Zika and a new non-addictive pain medicine. But he also talked about something that most of us hadn't thought much about, which is a universal vaccine for flu.

Now, that is something that you work on. I was surprised to learn that deaths from flu in the United States each year range from 12,000 to 56,000 individuals, compared to 493 from Tuberculosis, 19,000 from Hepatitis C, and 1 from Ebola. Flu is a real problem. You have a Center which monitors that and keeps after that at St. Jude's. Tell us about what you did with the H1N1 pandemic in 2009, the effect of the Center in keeping up with that, and

with subsequent outbreaks, and what your estimate is about whether we are likely to have a universal vaccine for flu.

Dr. SCHULTZ-CHERRY. Thank you, Senator. It's a fantastic question. During the 2009 pandemic, having one of the Centers for Excellence in Influence of Research and Surveillance allows us to be able to very much focus on emerging threats like the 2009 pandemic where we were able to very quickly identify the virus, make reagents for the virus that were distributed across the United States, as well as begin vaccine preparation. That is one thing that we have to do through our World Health Organization Collaborating Center is we make seed vaccine stocks for manufacturers and for the NIH.

And for the 2009, that was crucial in testing these seed stocks for safety and efficacy and it is something that we've continued to do, especially knowing that our vaccines are not as effective as we would like them to be, one of the reasons likely being is that we have a changing population, a lot more overweight and obese people and we know the vaccines do not work as well in this population.

So is a universal flu vaccine in the works? Absolutely. And is it something that we can accomplish? Yes, I think it is. I think it is realistic to think that we will have a vaccine that will provide some protection against the strains of influenza that we've currently identified as well as those that we haven't.

Again, we will have to—the virus is smarter than we are in many ways and can change very quickly, so it may require some changes to the vaccine, but we should be able to get much broader protection, including in our highest risk people, which are the very young, elderly, pregnant women, as well as overweight and obese people.

Senator ALEXANDER. Do you agree with Dr. Collins that could occur in the next decade?

Dr. SCHULTZ-CHERRY. Yes. I actually do. I think we are making great strides and there's many people focused on creating a universal flu vaccine. And I think it is something that can be accomplished.

Senator ALEXANDER. Thank you, Mr. Chairman.

Senator BLUNT. Senator Moran.

Senator MORAN. Mr. Chairman, thank you very much. Thanks to our panelists, our distinguished panel for being with us today. And you ought to take great satisfaction in the careers that you are pursuing. It's a noble cause and we are very grateful, this country and really as a world, for the efforts that you make.

I am interested in the number of people who have applauded Senator Blunt and Senator Murray in their efforts as well as Senator from Tennessee. And I certainly join in that. I also note how many times my colleagues have talked about how this is a bipartisan effort. That's certainly true. What is discouraging is that this is such an example of that. We highlight it because we are proud of it. It's been successful. It makes a difference, but we do that because it is the exception.

And if we like what we are doing in medical research and the bipartisan effort that we've engendered in order to accomplish that, we will have to try it elsewhere. And it might be just as enjoyable

and invoke additional pride in other aspects of what we do in Washington DC.

I also wanted to follow up on the appropriations process. We are pleased with what we have been able to do in the past appropriation bills, this subcommittee and the full appropriations committee with Chairman Cochran's leadership, in regard to NIH and research dollars. What that—that is a pyrrhic victory if we don't do the appropriation bill. And if we end up with another continuing resolution for 2017, all the things that we've bragged about as successes will be failure. And my hope, and I have spoken about this on the Senate floor and talked to my colleagues, and hope that there is a growing recognition that we have an opportunity to do something this year in the next few weeks.

We expect a Defense Appropriations Bill to come from the House, coming from the House to the Senate. We have passed MilCon-VA for fiscal year 2017. We will presumably pass a Defense Appropriation Bill for fiscal year 2017, but we need to take the next step and add the other 10 appropriation bills including Labor H so that the pat on the back that we give ourselves and the accolades that this subcommittee receives in regard to NIH actually come to fruition.

I would encourage Mr. Chairman—Chairman Cochran, I would work with you and Chairman Blunt as well as our Democratic colleagues to make sure we don't miss this opportunity for all 12 appropriations bills, the priorities that we've established, particularly here in the Labor H Bill actually become law. And then it sets the stage for us to do our jobs with fiscal year 2018.

So I hope that we can certainly take pride in what we've accomplished to date. We are pleased with where we've teed up this issue for the future, but we have an opportunity in just the next few weeks to take it a step further in which there's reality to our work for another year in a row and in my view would make a tremendous different for those who are encountering diseases and afflictions across the country and around the globe.

So I am here as a subcommittee member, as a member of the Appropriations Committee, to work with my Republican and Democrat colleagues, to work with Senator Cochran, the Chairman of our committee, to make sure that the appropriations process on our—is it 150th anniversary—150th anniversary fulfills its mission in establishing priorities and giving direction to an administration.

COMPREHENSIVE CANCER CENTER DESIGNATION

Let me address my question to Dr. Eberlein. We are your neighbor to the west. We have an NCI designated University of Kansas facility. We are in the process of attempting to receive the enhanced status. What does that mean? What could you—Siteman has received that designation, our neighbor to the east. What can I tell Kansans that if we are successful in being designated in such a manner that would mean to the people of Kansas?

Dr. EBERLEIN. Well, it is an opportunity to expand and enhance the cancer care throughout that region of the United States. It's bringing all of the resources of the University of Kansas and their collaborating partners, the Stowers Institute, other institutions, for the wellbeing of patients.

And that is—the NCI (National Cancer Institute) defines comprehensive slightly differently than most of us would think of comprehensive. We may think of it as being comprehensive in all types of cancer, but the way the NCI defines it is can you bring it bear all of the resources of all of the constituents in your locale for the betterment of patients with cancer. And so the University of Kansas is in the act of ability to do that and I think, yes, we've done that and we've tried to expand throughout Southern Illinois, the entire State of Missouri, et cetera, et cetera.

Senator MORAN. May I summarize that by saying that Kansans will have better opportunity for better treatment and a greater opportunity for cures in treatment of diseases?

Dr. EBERLEIN. Absolutely. And, again, it is—one of the great things about the National Cancer Institute Cancer Centers is the exchange of information, the collaboration, the exchange of patients for institutions that have specific clinical trials. And so, again, that is one of the benefits of the support of NCI designated cancer centers.

Senator MORAN. Mr. Chairman, I was apparently longer in my rhetorical efforts than I have time. I have a couple more questions. I don't know whether you intend to have a second round.

Senator BLUNT. We'll have a second round.

Senator MORAN. Okay.

Senator BLUNT. Let's do another second round of five-minute round. And, Senator Murray, do you want to start?

TRIPLE NEGATIVE BREAST CANCER

Senator MURRAY. Great. I just have a couple of questions. Dr. Eberlein, I wanted to ask you. I understand that since about 2007 breast cancer death rates have been steady in women younger than 50, and accounted actually for 90 percent of cases. Some of this is due to the fact that mammograms are less effective in younger women, but a lot can be attributed to the fact that younger women are more likely to get aggressive triple negative breast cancer which is obviously more difficult to treat.

Can you talk to us a little bit about what the state of efforts to develop effective precision medicine treatments for triple negative breast cancer is?

Dr. EBERLEIN. Absolutely. There's really two approaches, I think, in these younger patients who tend to have triple negative breast cancer. One is better imagining modalities and that is done through tomosynthesis, through MRI, and a judicious biopsy of abnormalities that are seen.

More specific to your second part of the question, precision medicine ways, we have actually developed markers for triple negative, so we can actually separate triple negative breast cancers into subcategories of breast cancer so that we are able to tailor the chemotherapy. And then we've also reversed the order of these treatments. Instead of doing surgery as a primary intervention, we do chemotherapy first.

I can tell you from firsthand experience, at least in our institution, 80 to 90 percent of these patients have dramatic responses to their chemotherapy upfront.

Senator MURRAY. Because it is designed specifically for that?

Dr. EBERLEIN. Because it is designed specifically for them. And it has two impacts. One is that it not only shrinks the disease, which actually makes my job doing surgery much easier, but it also eradicates the microscopic theoretical disease that is circulating looking for a home. And so we've actually seen a number of these patients who actually, at the time of their surgery, have complete pathologic responses. And so we are guardedly optimistic. It appears that patients are having actually better outcomes in the short-term, but that is, again, ongoing studies.

Senator MURRAY. That's exciting. Keep it going.

Dr. EBERLEIN. Thank you very much for the question.

RACIAL DISPARITIES IN DEMENTIA

Senator MURRAY. Yes. Dr. Grabowski, recent studies indicate that dementia incidents may be highest for African Americans and Native American populations. While some risk factors may be comparable across ethnic groups, we don't really know yet the risk factors and brain changes in their populations that may differ and there have been historical challenges, as I know, in recruiting diverse populations for some of our research studies. So it is going to be really critical to engage these and many other groups in a participatory way to ensure that questions can be answered while each population's cultural differences are appreciated and respected.

Can you talk a little bit about what kind of work your group is undertaking to reach out to those groups, and underserved populations, and what kind of studies you are conducting?

Dr. GRABOWSKI. Sure. So, addressing disparities, population disparities in Alzheimer research is one of the goals of the National Alzheimer Project Act.

At our institution for the last couple of years we've been building an exciting new effort creating a satellite core of investigation of Alzheimer disease in American Indians and Alaskan natives. So this is got two components. It's got a local urban Indian outreach component and it is got a more nationally focused aspect which arose from an opportunity that came out of the Strong Heart Study.

So Dr. Dedra Buchwald with Partnerships for Native Health is our collaborator and the leader of this particular effort, which reaches a group of, at this point, 450 American Indians that are reservation dwelling in Arizona, Oklahoma, and South Dakota, who were originally studied for heart disease risk and then cerebrovascular risk, and now for incidents of dementia. There's a lot of comorbidity in this population, so there's a lot of vascular disease, we are finding.

You're right. There was a Kaiser Permanente study published last year which showed that dementia incidents is higher in American Indians than in Caucasians and African Americans, as you mentioned, are particularly at risk. And other centers in the United States have particularly strong outreach programs in that direction, but our focus is on American Indians.

Senator MURRAY. Okay.

Dr. GRABOWSKI. Thank you.

Senator MURRAY. Thank you very much. Thank you, Mr. Chairman:

Senator BLUNT. Senator Cochran.

INSTITUTIONAL DEVELOPMENT AWARD

Senator COCHRAN. Mr. Chairman. Dr. Sasser, you mentioned in your testimony that your research has benefitted from the Institutional Development Award Program, which helps broaden geographic distribution of Federal research funding to States like Mississippi. Why is it important for biomedical research to take place in States like Mississippi where healthcare challenges are so significant?

Dr. SASSER. Thank you, Senator Cochran. I think this is a good follow up to Senator Murray's question because we do have health disparities in Mississippi. We have a high prevalence of obesity, high prevalence of kidney disease, high prevalence of cardiovascular disease. And then a lot of that is due to the high number of African Americans we have in our State.

So we do have to focus research efforts on treating these diseases in States like Mississippi because we see those firsthand. We have, being a biomedical researcher and a basic scientist, we have interactions with the clinicians who are actually seeing these diseases firsthand and we can think about ways to treat them more effectively. We have a long history of having excellent research at the University of Mississippi Medical Center and we are hoping to continue that by tapping into clinical populations to really understand why these diseases are so prevalent in States like Mississippi and how we can better treat those in the future.

Senator COCHRAN. Thank you.

Senator BLUNT. Senator Moran.

Senator MORAN. Mr. Chairman, thank you. And this is one more thought about the broad topic, particularly as we look at the Affordable Care Act and its reform and alteration. A long time before the Affordable Care Act was ever in place there was a Moran 10 Point Plan on trying to improve the access to affordable healthcare, one that never really received a lot of attention. But one of those 10 point plans was further investment into medical research. And a number of our panelists have indicated how this is also a money saving—we can reduce the cost of healthcare. And as we work on affordable healthcare issues we ought to be very cognizant of how important this aspect and the appropriations for NIH is.

YOUNG RESEARCHERS

So that I don't use up my own time and never get to ask my questions, I'll move forward. I wanted to highlight. One of the things that I was hoping you might say, Dr. Eberlein, and I would think this is true with comprehensive designation, but really with the focus on medical research. And I perhaps would address this to Dr. Sasser.

One of the things I would like to be a part of in my State is that young men and women who are interested in science and mathematics and engineering and research have a place to land. We educate them there and too often they find places to work elsewhere. And I would guess that comprehensive designation is helpful to us

in attracting and creating more opportunities and other facilities and researchers develop around those designations.

One of the things that our States share is that we are an IDEA State, IDEA State. And COBRA and EMBRE are important to us. And I wondered if you'd take a moment, Dr. Sasser, to talk about how we appeal to another generation of scientists and medical researchers so that this country finds the cures and treatments, but also remains a global powerhouse in science and research.

Dr. SASSER. Right. Yes. So, like I said, I have benefitted greatly from being a recipient of IDEA State funds. One of the reasons I moved to Mississippi after completing my post-doc is the great stability we have there. So I think, you know, as looking at careers, you want something that is going to be stable when you move your family there and get started.

So having those funds is very, very important. It's really helped me as I was embarking on my career to define a new area of research for my laboratory. It gave me the funds to have those pilot projects that eventually led to the receipt of my RO1. And in addition with attracting new students, those are very important too.

You mentioned the EMBRE program as well. We have students on our campus who are supported by the EMBRE, so when they're undergraduate research students they have the opportunity to come and see research firsthand, so that is very important. Additional programs like that include the R25 programs supported by the NIH that help bring students on our campus so we can expose them to those research careers.

In addition, I think it is very important, as you mentioned, to have this stable increase in funding for NIH. As we have these students on campus and we have graduate students, it is very important that they don't see their mentors and investigators ramming their heads against the wall year after year trying to get grants. They can see people have successful careers and see that as a stable opportunity. So, we are hoping that by increasing grant funding we can have more people who are able to take in these students to mentor them and then show them that this is a very rewarding career for them, for the potential training of the next generation, and then as well helping the healthcare of Americans.

Senator MORAN. Anyone else?

Dr. SCHULTZ-CHERRY. I think one important thing to point out is that the age of our first-time NIH investigators has changed. If you look since 1980 where predominantly less than people younger than 35 were having their first jobs, getting their first grants, we are now talking their mid-forties and there's more people in their late sixties with NIH funding than there are those people in their early forties. So it is really changed and it is affecting our trainees.

Senator MORAN. It perhaps is an opportunity to highlight the importance of elementary, middle school, high school, college education in regard to science and research mathematics. And it is not just NIH funding. It's what do we do to train another generation, and perhaps more importantly, enthuse another generation about science.

Dr. EBERLEIN. One of the most rewarding aspects of my job is we have an undergraduate program. We get about 350 applicants for the 15 positions that we carefully place in the researchers' labs.

And the letters that I receive from those individuals who say they hadn't found their passion, but now they did and that is what they're going to do the rest of their lives. And it is actually very rewarding to have those individuals and then track them through college, medical school. I have been there long enough now that that is an incredibly rewarding aspect of my position.

Senator MORAN. Thank you all very much.

Senator BLUNT. Senator Rubio.

PEDIATRIC GENOMIC RESEARCH

Senator RUBIO. Thank you. Thank you all for being here.

Dr. Eberlein, I have long had an interest. I am not sure I fully understand it from a scientific perspective, but I have long had an interest in genomics, genetic medicine, and the impact particularly on cancer. It's a fascinating—fascinated in your testimony about Dr. Werkman. Am I pronouncing it the right way, this particular case? I assume he's either a practitioner or research or both who himself was—and they were able to identify not just a specific characteristic of the genetic makeup of his cancer, but an off-label drug for kidney disease that was able to treat it.

So the promise of this is extraordinary and it leads to the notion that cancer isn't really one disease. It is a millions and millions of variations of it and very individual specific, so there's a tremendous amount of promise. And you also outline how that can make a difference in the treatment of breast cancer in your own practice where about only 20 percent of the people impacted by breast cancer would need chemotherapy in addition to radiation and surgery. Imagine if we could find who that 20 were, not just the impact on their lifestyle and the improvements in their care, but on costs, both to the healthcare system and to their lives. So this is very promising.

My question is: are we applying the same level of intensity and focus on an understanding of genomics and genetic medicine at the pediatric realm? Are we making the same progress on the pediatric realm as we are in the adult population? And if anyone else has a comment on that, I would love to hear about it as well.

Dr. EBERLEIN. Actually, we are. Washington University along with St. Jude actually mapped most of the genetic mutations associated with pediatric tumors. And the collaboration between St. Louis Children's Hospital, Washington University Siteman, as well as St. Jude's Research Institute have create a pattern looking at the pathways for the cause as well as spread of those tumors and have identified a number of novel targeted treatments.

So, again, it is actually been one of the more rewarding aspects of the areas of genomics. It's been particularly advantageous in the pediatric population and I think there's a plan for more investment, both at St. Louis Children's and Siteman Cancer Center as well as at St. Jude's.

Dr. SCHULTZ-CHERRY. Sure. I think the genomics has really revolutionized how we can look at pediatric cancers. And at St. Jude, the ability to go from bench to bedside, making those discoveries and then doing targeted medicine for pediatric cancers has really been amazing what's happened in the last 7 years since I have been there. It's really changing how we treat pediatric cancers.

TUMOR BANKS

Senator RUBIO. My understanding is there's an outside—just in the general realm of cancer there is a lot of collaboration nationally on tumor banks. I know there is, for example, one at the Moffitt Center in the Tampa Bay region. There's a lot of—everyone is capable. Is that information widely shared across the research?

Dr. EBERLEIN. Yes. Actually, there has been a lot of additional sharing among the institutions who, like Washington University and Siteman, have particular expertise in the genomic area that we have shared not only the genomic information—it is freely available to other institutions—but also with deidentified clinical information that is linked to that genomic information. And so these create very powerful databases that one can compare an individual patient with other patients with a similar type of fingerprint genomically and then develop an individualized treatment.

PRECISION MEDICAL AND FDA APPROVAL

Senator RUBIO. Well, so then the question I have is—and this is my final question given the time—I am just struggling to understand. How is the FDA process going to work if this medicine is so tailored at the individual level that there may be some—are the tweaks and the changes that would be required in treatments from patient to patient, does that apply? Do you foresee a point where the medicine and the treatments become so specialized and so specific and so different one from the other that it would require a separate FDA approval process that could complicate it and slow it down?

I mean I can—I don't know if I am describing it the right way, but if there are a thousand different ways to treat the same cancer and the medicines have a thousand different formulations as a result of that if they're significant enough, how does the FDA process account for that as we move forward?

Dr. EBERLEIN. Well, the FDA is actually expediting some of these personalized treatments. And again, to use Lucas Werkman's example, this was a drug that was FDA approved, but it was approved for the treatment of kidney cancer. In the case of Lucas, we identified that he had a specific point mutation that was the cause of his recurrent leukemia, not kidney cancer, but predicted that it would have response to this very targeted therapy which blocked the downstream impact of the gene mutation. And that is exactly what happened.

And so I think that it is a little bit of a change in paradigm for the FDA that some of these treatments will be applicable to a different patient, but the treatment will have been similar and the side effects, et cetera, would be similar.

OFF LABEL USES OF DRUGS

Senator RUBIO. And this is just a quick—is that the only time—is that the first time that that drug had been used off label for that purpose?

Dr. EBERLEIN. It has been the first time that it was used for a leukemia patient, yes, sir.

Senator RUBIO. And so was that—how does that now—is that now replicated? Has it been used again by others? How is that documented? How does that—does that count as a clinical trial? I mean, how does that work in terms of——

Dr. EBERLEIN. It would be as long as a patient has had whole genome sequencing and that specific mutation were in the patient. Then you would be able to use that drug off label.

Senator RUBIO. And why I asked that, Mr. Chairman, is because I can foresee where some insurers will push back on I am not going to approve a drug that is for kidney. He doesn't have a kidney problem. He has a leukemia issue. And so that is why it is so important to document its effectiveness.

Dr. EBERLEIN. Well, we've done exactly the same thing taking chemotherapy that is very effective in colorectal cancer and we identified that in about 20 percent of non-small cell lung cancer that the drug for colorectal cancer is actually very impactful. And so again, but only through genomics and comparing the genes and the sequences in the lung cancer patient and the colorectal cancer patient that we applied the colorectal drug to the lung cancer patient.

Senator BLUNT. Thank you, Senator Rubio.

You know, I think that is also an argument for a general view that this committee has recommended to our colleagues and has taken that you don't always know exactly what your research is going to turn up. And the Congress is, in all likelihood, not the best place to specifically talk about how research dollars are allocated, particularly how they're allocated over some longer period of time.

And I would say, particularly in response to the couple of very good observations, several good observations made about younger researchers, when you don't have an increase in NIH dollars, which we didn't have for 12 years, and you've got the commensurate decline in buying power, you have a decrease in real available dollars, and I think you referred to them, Dr. Sasser, as seasoned researchers who have an advantage. And Dr. Schultz-Cherry, you mentioned how the average age of researchers during that decade went up for I think pretty obvious reasons when you look at it which is why NIH, I believe on their own, determined with the increase that we did a couple of years ago that they were going to specifically designate part of that increase for young researchers to encourage people to stay in the field and know that there was opportunity there.

I would also say in response to the observation that Senator Alexander made when this committee increased by $2 billion the base number for research, that is $20 billion over 10 years. And then CURES added $4 billion to that, $4.5 billion over 10 years. So that is in a very short period of time a $24 billion increase.

And then as Senator Moran pointed out, if we can do the budget that we are all largely in agreement on for the year that we are already in, that is another $20 billion over essentially that same 10-year period. So suddenly we go from where we were to a $44.5 billion increase over a decade. And for young researchers and all researchers and all the opportunity, I think everybody on this subcommittee and frankly, Mr. Chairman, I think on our full committee are really committed to this being one of our priorities

which is why we are working so hard to see if we can't add that annual $2 billion, 20 over 10, sometime between now and the end of April when we deal in some long-term way for this fiscal year with where we are rather than just a CR. A CR from last year would have been a lot better for research than a CR from the year before that, but a second commitment where, as Senator Murray and I have said both, that you don't develop a pattern in year one. You have to start that pattern in year two and hopefully maintain that over the foreseeable future.

So, to our witnesses, thank all of you for being here. The subcommittee stands at recess.

SUBCOMMITTEE RECESS

[Whereupon, at 12:01 p.m., Wednesday, March 8, the subcommittee was recessed, to reconvene subject to the call of the Chair.]